THE BULLETIN OF Mathematical BIOPHYSICS

JUNE 1950

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 12 · · · · · NUMBER 2

$$f(x, \delta_1, \delta_2) = \frac{x}{\delta_2 - \delta_1}\left[\frac{1}{k_1+1}\int_{\delta_1}^{(k_1+1)y} d\delta + \frac{1}{k_1+2}\int_{(k_1+1)y}^{(k_1+2)y} d\delta + \cdots \frac{1}{k_2+1}\int_{k_2 y}^{\delta_2} d\delta\right] = \frac{xy}{\delta_2 - \delta_1}\left[\frac{\delta_2 x}{k_2+1} - \frac{\delta_1 x}{k_1+1} + \frac{1}{k_1+2} + \frac{1}{k_1+3} + \cdots \frac{1}{k_2+1}\right]. \tag{16}$$

By the inequalities (15), we have

$$\operatorname*{Lim}_{x\to\infty} \frac{\delta_2 x}{k_2+1} = \operatorname*{Lim}_{x\to\infty} \frac{\delta_1 x}{k_1+1} = 1. \tag{17}$$

We thus have for large values of x

$$\begin{aligned} f(x) &\sim \frac{1}{\delta_2 - \delta_1}\left[\frac{1}{k_1+2} + \frac{1}{k_1+3} + \cdots \frac{1}{k_2+1}\right] \\ &\sim \frac{1}{\delta_2 - \delta_1}\left[\log(k_2+1) - \log(k_1+1)\right] \\ &\sim \frac{1}{\delta_2 - \delta_1}\log\frac{\delta_2}{\delta_1}. \end{aligned} \tag{18}$$

We have proved

THEOREM 2. *The rectangular distribution function of refractory periods*

$$N(\delta) = \frac{1}{\delta_2 - \delta_1} \text{ for } 0 < \delta_1 \leqq \delta < \delta_2$$
$$= 0 \text{ elsewhere}$$

gives rise to an output intensity function which tends asymptotically to the value $(\delta_2 - \delta_1)^{-1} \log (\delta_2/\delta_1)$ *as* x *grows without bound.*

The asymptotic value of the output intensity determined by the distribution function (14) is, of course, a function of the parameters of the aggregate, namely, the minimum and the maximum refractory periods in it. If we hold the minimum fixed, we can see how the output intensity varies with the range (or spread) of the refractory periods in the aggregate. We see that as the range narrows down to zero, the limiting value of the output intensity becomes

$$\operatorname*{Lim}_{\delta_2\to\delta_1} \frac{1}{\delta_2 - \delta_1}\log\frac{\delta_2}{\delta_1} = \frac{1}{\delta_1} \tag{19}$$

as should be expected, since giving every neuron in the aggregate the same refractory period is equivalent to considering the behavior of a single neuron. On the other hand, as the range increases, we have

$$\lim_{\delta_2 \to \infty} \frac{1}{\delta_2 - \delta_1} \log \frac{\delta_2}{\delta_1} = 0, \quad \delta_1 > 0. \tag{20}$$

Thus the output intensity vanishes as the spread of refractory periods increases without bound. If, however, the thresholds of the neurons are proportional to their refractory periods, so that the *total number* of the neurons involved in responding to the input is proportional to the range of δ, then the *total output* $F(\delta_1, \delta_2)$, according to Definition 2 above, will be obtained by multiplying the output intensity by $\rho(\delta_2 - \delta_1)$ where ρ is a constant of proportionality. Then

$$F(\delta_1, \delta_2) = \rho \log \frac{\delta_2}{\delta_1}. \tag{21}$$

This is a "mobilization" picture of growing excitation, where more neurons come into play as the input intensity increases. If δ_1 is fixed, and δ_2, being the upper limit of the refractory periods, proportional to the upper limit of the thresholds and therefore to the input intensity, then the total output as a function of input *intensity* follows the Weber-Fechner law.

It is easy, of course, to get the logarithmic input-output curve in another, more obvious way, if one employs the pure "mobilization" model.

In this model each neuron responds with a certain frequency characteristic for it independently of the input frequency, provided the latter exceeds a certain threshold. The increased total output of an aggregate accompanying an increased input is due entirely to "mobilization," that is the involvement of more and more neurons as their threshold frequencies are exceeded by the input. Suppose now that the thresholds in the aggregate are so distributed that their frequency of occurrence is inversely proportional to their magnitude h in a finite range:

$$\begin{aligned} N(h) &= c/h \quad \text{for} \quad h_1 \leqq h \leqq h_2 \\ &= 0 \text{ elsewhere,} \end{aligned} \tag{22}$$

where $c = [\log (h_2/h_1)]^{-1}$ is the proper normalization constant. Then if the input intensity x is just sufficient to fire the neurons with threshold $h(x)$, then all the neurons with thresholds below h will

respond with their characteristic output intensity K, which we here suppose the same for all neurons, and the total output of the aggregate will be

$$F(x) = K \int_{h_1}^{h(x)} N(h)\,dh = A \log \frac{h}{h_1}, \tag{23}$$

where $A = Kc$. If we further assume that h is proportional to x, (23) becomes

$$F(x) = A \log (kx) \tag{24}$$

where k is another constant.

This model can be generalized by dropping the restrictions on $h(x)$ and making the response frequency of each neuron a function of both its threshold and of the input frequency. In this case

$$F(x) = \int_{h_1}^{h(x)} K(h, x) N(h)\,dh \tag{25}$$

which by a change of variables can be put into a form of Volterra's integral equation of the first kind. Considerations involving refractory periods can be incorporated into the kernel of the equation (which describes the behavior of the individual neuron). If the refractory periods are associated with the thresholds by some functional relation $\delta = \delta(h)$, we have an integral equation of an even more general type,

$$F(x) = \int_{\delta(h_1)}^{\delta[h(x)]} \int_{h_1}^{h(x)} K'(h, \delta, x) N(h) N'(\delta)\,dh\,d\delta, \tag{26}$$

where $N'(\delta)$ is the frequency distribution with respect to δ. Clearly, equation (2) is a very special case of (26).

The Distribution $\mathrm{N}(\delta) = \mathrm{k}^2\,\delta\,\mathrm{e}^{-\mathrm{k}\delta}$.

We shall examine one more type of distribution with respect to refractory periods, namely

$$N(\delta) = k^2\,\delta\,e^{-k\delta}. \tag{27}$$

Here the output intensity is given by

$$f(x) = k^2 x \sum_{n=1}^{\infty} \frac{1}{n} \int_{(n-1)y}^{ny} \delta\,e^{-k\delta}\,d\,\delta, \tag{28}$$

which upon integration yields

$$f(x) = k^2 x \left\{ \left[\frac{-y}{k} e^{-ky} - \frac{1}{k^2} e^{-ky} \right] + \frac{1}{2} \left[\frac{-2y}{k} e^{-2ky} - \frac{1}{k^2} e^{-2ky} \right] \right.$$
$$+ \frac{1}{3} \left[\frac{-3y}{k} e^{-3ky} - \frac{1}{k^2} e^{-3ky} \right] + \cdots.$$
$$+ \frac{1}{2} \left[\frac{y}{k} e^{-ky} + \frac{1}{k^2} e^{-ky} \right] + \frac{1}{3} \left[\frac{2y}{k} e^{-2ky} + \frac{1}{k^2} e^{-2ky} \right]$$
$$\left. + \cdots\cdots\cdots + \frac{1}{k^2} \right\}$$

and after rearrangement of terms,

$$f(x) = k^2 x \left[\frac{-y}{k} \sum_{n=1}^{\infty} \frac{e^{-nky}}{n+1} - \frac{1}{k^2} \sum_{n=1}^{\infty} \frac{e^{-nky}}{n(n+1)} + \frac{1}{k^2} \right]$$
$$= x \left[1 - \sum_{n=1}^{\infty} \frac{e^{-nky}}{n(n+1)} \right] - k \sum_{n=1}^{\infty} \frac{e^{-nky}}{n+1}. \tag{29}$$

If we let $e^{-ky} = z$, and thus $x = -k/\log z$, the right side of (29) may be represented by

$$-k \left[\frac{z \log(1-z) - \log(1-z) - \log z \log(1-z)}{z \log z} + 1 \right] \tag{30}$$

as may be seen by expanding (30) in power series. We are interested in the limiting value of the expression (30) as x tends to infinity, that is, y tends to zero, and z tends to unity. After several applications of l'Hôpital's rule, it turns out that the limit of the expression in the bracket of (30) is -1, that is

$$\lim_{x \to \infty} f(x) = k. \tag{31}$$

Since the mode of δ in the distribution (27) is $\bar{\delta} = 1/k$, we see that the entire aggregate behaves in the limit as a single neuron whose refractory period is $1/k$. It can be shown, however, that the function (30) is monotone increasing with respect to x, so that the oscillations which the output intensity of the single neuron exhibits are "smoothed out" in the aggregate.

The same method can be used to compute the output intensity function and the limiting values thereof for other forms of the distribution.

Randomization of Stimulus Intervals.

If we suppose that a neuron is a primary receptor, that is, re-

ceives stimuli directly from the outside, it is reasonable to randomize the intervals between the incoming stimuli. For example the stimuli can be light quanta or some other form of radiation.

Suppose that the distribution of the incoming stimuli in time is a Poisson distribution, that is, if an instant is picked at random the probability distribution of the time of the next stimulus will be given by

$$P(x, \tau) = xe^{-x\tau}, \tag{32}$$

where x is independent of time and τ is the interval between the chosen instant and the next stimulus. Clearly (32) is also the probability distribution of the interval between two successive stimuli. Furthermore the expected interval is given by

$$\int_0^\infty x\tau e^{-x\tau} d\tau = 1/x, \tag{33}$$

so that x is seen to be the input intensity.

R. Jost (1947) gives the relation between input and output intensities of a counter with a refractory period, which in our notation is as follows:

$$f(x) = \bar{x}\left[1 + \int_0^\delta x dt\right]^{-1}, \tag{34}$$

where $\bar{x}$ is the average input intensity over the entire time range. If $P(x, \tau)$ is given by (32), $\bar{x} = x$ and (34) reduces to

$$f(x) = x(\delta x + 1)^{-1}. \tag{35}$$

However Jost's formula holds in the general case where x is a function of time.

In the simple case of the Poisson distribution where x is independent of time, (35) can be derived from very elementary considerations. Note that the expected time of the next stimulus is $1/x$ regardless of what instant is chosen. In particular if the origin of time is chosen at the instant when the neuron fires and the expected time of the next impulse is measured from δ, the refractory period of the neuron, then the expected time of the next firing measured from the origin will be $\delta + 1/x$, and hence the output intensity will be given by $(\delta + 1/x)^{-1}$, which is the right side of (35).

It is important to note that the probability distribution of the intervals between successive firings will in this case *not* be of the form (32), since if a firing instant is chosen, the probability of the next firing will be zero for the next interval of time of duration δ. In fact in the extreme case, where the neuron is firing with its limit-

ing frequency $1/\delta$, this distribution becomes the Dirac function with the peak at some point between zero and δ, depending on the instant chosen. If the instant chosen as origin is not specified (chosen at random), then the distribution is seen to be rectangular

$$\begin{aligned} P(t) &= 1/\delta \text{ for } 0 \leqq t \leqq \delta \\ &= 0 \text{ elsewhere.} \end{aligned} \tag{36}$$

The intermediate cases are represented by functions ranging from (32) to (36).

We shall need these probability distributions in our discussion of filter nets. However their derivation will be postponed at this time, and we shall construct the simplest sort of a filter net, where the refractory period of each neuron is zero.

The Filter Net.

A filter net is an arrangement of neurons in which certain neurons are able to respond to only a finite range of input intensity of outside stimuli. Such a net is shown in Figure 3.

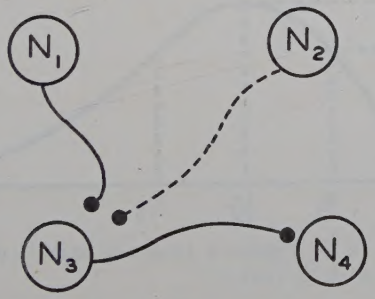

FIGURE 3. A simple filter net.

Neurons N_1 and N_2 in Figure 3 receive randomized stimuli from the outside. Neuron N_1 excites N_3, but N_2 inhibits N_3 provided N_3 receives a stimulus from N_2 within an interval σ before it receives a stimulus from N_1, in which case the stimulus from N_1 fails to excite N_3. In short N_3 fires at the instant t, if it receives a stimulus from N_1 at that instant (synaptic delay is not considered) and if it has not received a stimulus from N_2 at the time τ, such that $t - \sigma \leqq \tau \leqq t$.

Now the probability of receiving a stimulus from N_1 in the infinitesimal interval dt is xdt, where x is the input intensity from the

outside. Moreover, because of (32) the probability of *not* having received a stimulus from N_2 during the interval σ is $e^{-x\sigma}$. This is so because $xe^{-x\sigma}dt$ is the probability of the immediately preceding impulse from N_2 occurring between σ and $\sigma + dt$ before t. Now xdt is the probability of a stimulus at an arbitrary instant. Therefore $e^{-x\sigma}$ is the probability that no stimulus has occurred within σ.

Hence the probability of firing of N_3 at a given instant is given by

$$f(x, \sigma)\,dt = xe^{-x\sigma}dt \tag{37}$$

and hence $xe^{-x\sigma}$ represents the output intensity. It is seen to be a monotone decreasing function of σ, but it has a maximum with respect to x, namely at $x = \sigma^{-1}$, where the output intensity is $(e\sigma)^{-1}$.

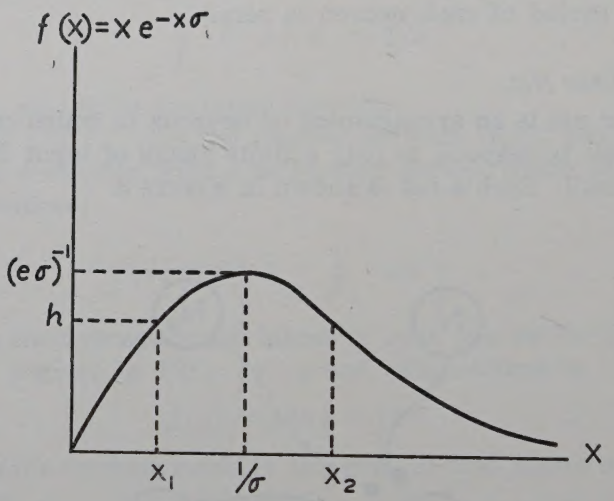

FIGURE 4. Neuron N_4 in Figure 3 responds only to outside input frequencies between x_1 and x_2 if $0 < h \leqq (e\sigma)^{-1}$.

Let now neuron N_4 have a threshold h, such that $0 < h < (e\sigma)^{-1}$. As can be readily seen from Figure 4, N_4 will respond to *outside* input frequencies only between the limits shown. As h increases and approaches $(e\sigma)^{-1}$ the range of response of N_4 diminishes, and the neuron gradually turns into a "discrimination" neuron, able to respond to practically a single frequency. If h increases still further, N_4 fails to respond altogether and the filter net breaks down.

This work was aided by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago, and from The Lucius N. Littauer Foundation to The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 12, 1950

ON BLAIR'S THEORY OF EXCITATION AND THE ROLE OF INTERNAL ENERGY SOURCES

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It is shown that Blair's theory of excitation is independent of, and consequently valid for, any possible relationship between the threshold and the magnitude of the stimulus. It is pointed out that if a dependence of threshold on stimulus is assumed, the concept of rheobase becomes meaningless. Consequently, contrary to Blair's impression, the disagreement between his theory in its original form and the experimental data on the time of incipient excitation with constant stimulus (response time) cannot be explained by assuming a dependence of the threshold on the magnitude of the stimulus. It is shown that a modification of Blair's interpretation, obtained by taking into account effects of internal energy sources released by the stimulus, eliminates the disagreement mentioned above between theory and experiment. The role of such modification in connection with propagation of excitation is discussed.

The Blair theory of excitation is based, as it is well known, on the differential equation

$$dc/dt = \sigma I - \rho c\,, \tag{1}$$

where I is the magnitude of the external stimulus (e.g. intensity of a constant current applied to a nerve), c is the magnitude of some effect of the stimulus in the biological system considered and σ and ρ are two constants, the first measuring the susceptibility of the system to the stimulus I, the second its ability to react to the effect c of the stimulus. If the magnitude of the stimulus I is constant, the explicit solution $c(t)$ of equation (1), under the condition $c(0) = 0$, is:

$$c(t) = (\sigma/\rho) I (1 - e^{-\rho t}). \tag{2}$$

The condition $c(0) = 0$ is inherent to the definition of c itself. The assumption that a threshold magnitude h of c is necessary to cause excitation leads to the following theoretical expression of the minimum value R of I required for excitation:

$$R = (\rho/\sigma) h\,. \tag{3}$$

This is the threshold stimulus, the so-called rheobase, whose appli-

cation for an infinite length of time would excite the system by bringing c from zero up to its threshold value h. If a constant stimulus I is applied which is larger than R, the duration τ of application of such stimulus required to produce excitation is, from previous equations:

$$\rho\tau = \ln[I/(I-R)]\,. \tag{4}$$

In the derivation of all the above relations the only assumptions made concerning the threshold h *of* c *are that this threshold exists and that it does not change during the application of the stimulus. No assumption of any kind is made as to a possible dependence of the threshold* h *on the magnitude* I *of the stimulus. Consequently, all the relations written above are valid without any change, even if* h *is assumed to be dependent on* I *in any fashion whatsoever.* In other words, relation (4), *exactly* as it is written, is *an unavoidable consequence of the theory.* It is known that this relation does not agree entirely with experiments, which can be fitted, however, by the formula:

$$\rho\tau = \ln[I/(I-R)] + C\,, \tag{5}$$

where C is a constant. Blair thought that this fact did not contradict his theory, but that it simply meant that the threshold h depended on the magnitude I of the stimulus. The argument which we just presented shows that his reasoning must contain an error. Apparently he did not notice that his general theory, including formula (4), is independent of, and consequently valid for, any possible relationship between the magnitudes of the threshold h and of the stimulus I. None of his formulae can be changed by assuming a particular dependence of h on I, consequently none of such possible dependences can make an additive constant appear on the right-hand side of formula (4).

The question arises—which exactly is the erroneous step in Blair's reasoning? The answer can be given in the following form: If the threshold h of c is assumed to be dependent on the magnitude I of the stimulus, the concept of rheobase, and consequently also any formula containing it, becomes meaningless. In fact, the rheobase R is defined as the minimum magnitude of a time-independent stimulus I causing excitation, i.e. as the minimum value of I, constant in time, which is able to bring c from zero to its threshold value h. Therefore, if h is dependent on I, rheobase R is also dependent on I, that is, R is a *function* of I and consequently cannot be a *minimum* of I!

Another form of presenting the argument is the following: Since

relation (5) is experimentally correct, one may ask what are the implications of formula (5) and of all the other formulae of Blair's theory with exception of formula (4); in other words, what are the consequences of equations (1) to (3) combined with equation (5)? To answer this we note that from formula (5) the following relation can be easily derived by elementary algebra:

$$e^{-\rho\tau} = e^{-c}\,[1 - (R/I)]\,. \tag{6}$$

But from equation (2) we have by definition of h and τ:

$$h = (\sigma/\rho)I(1 - e^{-\rho\tau}),$$

which becomes by equation (6):

$$h = (\sigma/\rho)I(1 - e^{-c}) + (\sigma/\rho)Re^{-c},$$

and by equation (3)

$$h = (\sigma/\rho)I(1 - e^{-c}) + h\,e^{-c}.$$

From here $h = (\sigma/\rho)I$, which, compared with equation (3), gives $R = I$, that is, any magnitude of applied stimulus would be the rheobase, which is impossible, because I is a variable and R is a constant by their physical and physiological meanings. This conclusion is logically inconsistent because it is derived from mutually incompatible facts—equation (5) and Blair's theory. It can be added to this argument that since Blair's reasoning implies $I = R$, equation (5) contains a term $\ln \infty$ and is consequently meaningless. However it should not be inferred from here that the error under discussion lies in an inappropriate application of a mathematical procedure; it is of a purely logical nature.

While pointing out that equation (5) cannot be put into agreement with Blair's theory by assuming a dependence of the threshold of c on the magnitude of the applied stimulus, we should keep in mind that Blair's theory describes a surprising amount of facts with extremely simple means. In view of our very incomplete knowledge of the nature of neurophysiological phenomena it is not surprising that the few elementary thoughts from which Blair succeeded in developing a theory make the latter sometimes diverge from experimental facts. Although he himself indicated at one time that the constant C may not represent any essential part of the mechanism of the process, but may be perhaps only an expression of a perturbation due to electrodes, it seems worthwhile to examine whether the disagreement under discussion cannot be connected with some more fundamental fact since many experiments have been analyzed in the

literature in connection with that constant C.

Blair himself pointed out a possibility for modifying his theory so as to lead to relation (5) with $C \neq 0$. In fact, if we assume that there is a *latency* or a *time lag* between the effect and the stimulus, we have to use a condition of the type $c(t) = 0$ for $t < t_0$ instead of the condition $c(0) = 0$ where t_0, the time lag, is a non-negative quantity. We then obtain from the differential equation (1), under the assumption of a constant stimulus I,

$$c(t) = (\sigma/\rho) I[1 - e^{-\rho(t-t_0)}] . \tag{7}$$

This equation, with the additional condition,

$$c(t) = 0 \quad \text{for} \quad t < t_0$$

would now replace relation (2). The rheobase would be still given by equation (3) which follows also from relation (7). But instead of equation (4) we would have:

$$\rho \tau = \ln [I/(I - R)] + \rho t_0 .$$

A comparison of this with equation (5) gives

$$C = \rho t_0 ,$$

which is positive. But in 54 out of 65 sets of experimental data analyzed by Blair the constant C comes out negative. [The constant C in Blair's papers equals $-C$ of this paper. N. Rashevsky (1948, p. 282) uses the symbol C_1 for our C; there is apparently a misprint on that page since the constant C_1 is negative for the data given on the same page.] Thus the concept of latency cannot be accepted within the framework of Blair's theory.

The constant C is obtained as an intersection of a straight line obtained by plotting experimental data on $\ln [I/(I - R)]$ against τ. Consequently experimental data on small values of τ are important for the determination of C. As a matter of fact Blair's data go much below 1 millisecond and the question arises whether during such short intervals of time after the closure of the circuit the transient may be sufficiently important so as to cause an appreciable deviation of the intensity of the current from its asymptotically constant value, since constant current is assumed in the theory. According to H. J. Curtis and K. S. Cole (1944) the membrane resistance of a squid giant axon is 1000 ohm/cm^2, the membrane inductance is 0.2 henry/cm^2. The transient in an inductive circuit is given by:

$$I = I_a(1 - e^{-rt/L}), \tag{8}$$

where I_a is the asymptotic value of the current intensity on which theoretical calculations are based and r and L are the resistance and the inductance of the circuit. Assuming the above values of r and L we obtain from (8), for $t = \frac{1}{2}$ millisecond: $I \approx 0.918\ I_a$. Thus the effect of the transient would amount to some 8% of the intensity of the current, if one neglects the effect of the part of the circuit external to the biological system under experimentation. Since according to Cole et al (cf. Cole and Baker, 1941, p. 799; Curtis and Cole, 1944, p. 805) the axoplasm and the intercellular fluid contribute to the resistance of the nerve but not to its inductance, it is likely that the actual transient is smaller than the above value. In this very crude estimate of the transient we have also neglected a possible capacity effect. It is easy, however, to show that a transient due to a small inductance would not lead to a formula of type (5) with a negative constant C. In fact, if we solve the differential equation (1) of Blair's theory on the basis of the current (8) we obtain:

$$c = \sigma I_a \left[\left(\frac{1}{\rho} - \frac{1}{\rho - \lambda} \frac{1}{e^{\lambda t}} \right) + \left(\frac{1}{\rho - \lambda} - \frac{1}{\rho} \right) e^{-\rho t} \right],$$

where $\lambda = r/L$. Since λ is very large, because the inductance is very small with respect to the resistance, we neglect the second term in the first parenthesis and obtain:

$$c \approx \frac{\sigma I_a}{\rho} \left[1 - \frac{\lambda}{\lambda - \rho} e^{-\rho t} \right]. \tag{9}$$

The rheobase considered as the minimum value of I_a causing excitation is still given by $R = (\rho/\sigma)h$. Consequently, from equation (9) the following formula is obtained for the response time:

$$\rho\, \tau \approx \ln \frac{I_a}{I_a - R} + \ln \frac{\lambda}{\lambda - \rho}$$

with $C = \ln [\lambda/(\lambda - \rho)]$, but this constant C is never real and negative.

The concept that energy stored in some form in the nerve is released by the stimulus to work toward excitation is well known (Curtis and Cole, 1944, pp. 798–808; Lorente de Nó, 1947, pp. 440–441). It can be easily seen that such *energy sources* if taken into account in a suitable form together with Blair's theory lead to equation (5) with a negative constant C as required by experiments. In fact, it is intuitive to assume that the amount of such internal energy re-

leased by the stimulus is proportional to the magnitude of the latter, within certain limits at least. Since Blair's theory assumes that applied current produces some effect in the nerve which leads to excitation, it is natural to assume that those internal energy sources produce the same effect when released, to some extent at least. We are lead in this way instead of equation (2) to the following relation:

$$c(t) = (\sigma/\rho) I (1 - e^{-\rho t} + \alpha), \tag{10}$$

where α is a constant. The quantity $(\sigma/\rho) I\alpha$ measures the contribution of the internal energy sources to the effect c. The relation between the rheobase and the threshold is now:

$$h = (\sigma/\rho) R (1 + \alpha), \tag{11}$$

which substituted into equation (10) gives for the response time τ:

$$\rho \tau \ln [I/(I - R)] - \ln(1 + \alpha). \tag{12}$$

This is exactly equation (5) with a negative C, because α is positive. In connection with equation (10) we have to assume that the internal energy is released during a certain very short interval of time between the moment of application of the current ($t = 0$) and the smallest response time τ encountered in the experiments under consideration. Thus the release of energy whose effect appears in equation (10) would occur within a time t_E smaller than 1/2 millisecond. Equation (10) would be valid for $t \geqslant t_E$. Since for the purpose of the present discussion we are not interested in magnitudes of c for $t < t_E$, we can leave out of consideration the question of how fast that energy is released within that time t_E.

To test this idea of internal energy sources in the form here presented, let us examine whether it can be applied to the phenomena of propagation of excitation in a nerve fiber. We will follow the method applied by N. Rashevsky in chapter xxvii of his book (1948), in which he schematized the nerve fiber as a semi-infinite core conductor of radius S surrounded by a thin shell of thickness δ and imbedded in a medium whose resistance is γ times smaller than the resistance of the core of the same length. Under the assumption of a steady state, neglecting any possible contribution of internal energies, the intensity of the current is given by the equation

$$I = I_0 e^{-\beta x}, \tag{13}$$

where I_0 is the intensity of the current at $x = 0$ and

$$\beta^2 = \frac{2r_c}{\delta r_s S}\left(1 + \frac{1}{\gamma}\right),$$

with r_c the resistivity of the core and r_s the resistivity of the shell. The condition of excitation is $I \geqslant R$. Taking into account equations (11) and (13) it is seen that the excitation would occur only within the range of x:

$$x \leq \frac{1}{\beta} \ln \frac{I_0 \sigma (1 + \alpha)}{h \rho}. \tag{14}$$

We can estimate this range by using the values of the constants based on H. A. Blair's experiments as suggested by N. Rashevsky (1948, p. 329), $\beta \approx 1$, $h\rho/(I_0\sigma) = 1/2$. If there were no internal energy sources ($\alpha = 0$) the excitation would propagate only within $x \leq \ln 2 \approx 0.7$ cm. A larger intensity of current I_0 would be necessary to cause excitation beyond that range of x. With internal energy sources α is positive and the range is larger. For instance, with a value of $C = -\ln(1 + \alpha) = -0.4$, which is about the maximum value of C derived by Blair from his previously mentioned experiments, we obtain $\alpha = 1/2$ and the range within which the excitation would propagate comes out to $x \leq 1.1$ cm. It should be noted that a value of $\beta = 1$ on which the above calculations are based implies a very low ratio of r_c/r_s (cf. Rashevsky, 1948, p. 329). If this ratio is increased, β is also increased and x is decreased. At the same time it should be kept in mind that a value of $\alpha = 1/2$, which represents the contribution of the internal energy sources to the magnitude of c, amounts to 50% of the value that c would acquire asymptotically at $t = \infty$ if those energy sources were not acting [cf. equation (10)]. Thus there seems to be no reason to consider a higher value of α. Besides this, if the rheobase is determined directly by experiments the analysis becomes completely independent of α. In fact, we obtain from equations (11) and (14) for the excited length of the nerve

$$x = (1/\beta) \ln (I_0/R). \tag{15}$$

It is seen in this way that taking into account the internal energies through a term α in equation (10), in agreement with some experimental facts, is however insufficient to explain the phenomena of propagation of excitation.

The contribution of internal energies to propagation of excitation in the nerve has been taken into account successfully by N. Rashevsky in a different manner. We would like to show how his results can be easily derived from the previous formulae. For this purpose let us note that by substituting equation (13) into (12) we obtain:

$$\rho \tau = -\ln (I_0 - R\, e^{\beta x}) + \ln I_0 - \ln (1 + \alpha)$$

which, differentiated with respect to τ, gives the velocity of propagation of excitation:

$$\dot{x} = (\rho/\beta)\,[(I_0/R)\,e^{-\beta x} - 1]\,. \tag{16}$$

It may be easily seen from equation (15) that at the end of the range within which the excitation propagates the velocity $\dot{x}$ becomes zero as it should be, mathematically. We have seen that the shortness of this range contradicts the experimental facts. Rashevsky, however, takes into account the contribution of the internal energies by assuming that the curve representing the intensity of the current, instead of being expressed at each moment by equation (13), is rigidly displaced along the nerve fiber with $x = 0$ always at the point of excitation. Under this assumption it is easy to see that excitation propagates with a constant velocity. In fact, if at a certain moment t the excitation reaches a point x, the velocity of propagation of excitation at that moment depends on the magnitude that c has in an infinitesimal region dx immediately ahead of the excited point and on the magnitude that c will have in the same region during an infinitesimal interval of time dt immediately following t. But in that region and during that interval of time c varies between $[c(x,t)]_{exc}$ and

$$[c(x,t)]_{exc} + \left[\frac{\partial\, c(x,t)}{\partial\, x}\right]_{exc} dx + \left[\frac{\partial\, c(x,t)}{\partial\, t}\right]_{exc} dt, \tag{17}$$

where the subscript *exc* indicates that the functions in the brackets are calculated at that time t at which the point x becomes excited. We will show that all the above terms in brackets are constant, which will prove that immediately ahead of the excited point, in time and in space, c has always the same value. This will prove that the velocity of excitation is a constant, because this velocity depends only on the magnitude of c immediately ahead of the excited point. Now, by the definition of the process of excitation itself we have:

$$[c(x,t)]_{exc} = h = \text{constant}\,.$$

To prove that the two derivatives in equation (17) are also constant, it is convenient to introduce a symbol for the distance covered by the excitation during a time t, viz.: $\xi(t)$. The symbol ξ concerns in a sense the same quantity as x, except that x represents any point of the axis whereas $\xi(t)$ expresses the relationship between that point and the time of its excitation. Thus x is an independent variable and $\xi(t)$ is a function. Since we disregard at present a possible

contribution of the internal energy sources through the factor α, we obtain from equations (12) and (13), putting $x = \alpha = 0$,

$$\rho t_0 = \ln [I_0/(I_0 - R)],$$

for the time of excitation t_0 of the point $x = 0$. Thus $\xi(t) = 0$ for $t \leq t_0$. Assuming Rashevsky's hypothesis of the rigid displacement of the current (13) together with the excitation, the explicit expression for the intensity of the current as the function of x and t becomes:

$$I = I_0 e^{-\beta x + \beta \xi(t)}.$$

Substituting this into the general formula for the solution of the differential equation (1), i.e. in:

$$c = \sigma e^{-\rho t} \int_0^t I(t') e^{\rho t'} dt',$$

we obtain:

$$c(x, t) = I_0 \sigma e^{-\rho t - \beta x} \int_0^t e^{\rho t' + \beta \xi(t')} dt'. \tag{18}$$

From here we easily derive

$$\partial c(x, t)/\partial x = \beta c(x, t);$$
$$\partial c(x, t)/\partial t = -\rho c(x, t) + I_0 \sigma e^{\beta \xi(t) - \beta x}.$$

But at the moment of excitation of x we have:

$$c(x, t) = h, \qquad \xi(t) = x,$$

the latter by the definition of the function $\xi(t)$ itself. Thus the terms in brackets in equation (17) are constant in time and space and if we think of the excitation as a pulse propagating along the nerve, the situation ahead of the pulse would be always the same as it was at $t = t_0$ ahead of $x = 0$. Consequently the velocity of the pulse would be always equal to its initial value at $x = 0$. But this value is immediately obtained from the previous theory of excitation because at the moment of excitation of $x = 0$ the quantity c is the same throughout the whole nerve fiber in both theories. We get in this way, putting $x = 0$ in equation (16):

$$\dot{x} = (\rho/\beta)[(I_0/R) - 1].$$

This is Rashevsky's formula. It may be added that this formula is in quite good agreement with experiments. In fact, taking into account the expression of β, it is easy to see that the above formula implies a direct proportionality of the velocity of propagation to the

square root of the diameter. R. J. Pumphrey and J. Z. Young (1938) experimenting on nerve fibers of Cephalopods in the range of 30 to 718μ found a proportionality of the velocity to the power 0.614 of the diameter. J. B. Hursh (1939) and H. S. Gasser and H. Grundfest (1939), experimenting with nerve fibers of cat and kitten, and cat and rabbit respectively, within ranges up to about 20μ of diameter, found a proportionality of the velocity to the first power of the diameter or slightly less than that. The older experiments by H. S. Gasser and J. Erlanger (1927) imply also the same type of relationship. The hyperbolic relationship between the velocity and the rheobase or the threshold is also confirmed by experiments (Fulton, 1947, p. 102). Thus there are several experimental results which agree with Rashevsky's formula.

This work was aided by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago and from the William T. Morris Foundation to The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 12, 1950

SOME CELLULAR DIFFUSION PROBLEMS BASED ON ONSAGER'S GENERALIZATION OF FICK'S LAW

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Some consequences of Onsager's generalization of Fick's law are examined. It is found that *metabolized* solutes may flow continually against their concentration gradients. *Inert* solutes may exist in a higher or lower concentration inside of the cell than in the medium thus appearing to be accumulated or excluded. The magnitudes of such concentration differences are dependent upon the rates of metabolism of metabolized solutes. Alteration of these rates may *further* increase the concentration disparity by causing inert solute to flow from a low to a high concentration. Due to the mutual dependence, demanded by Onsager's law, of the diffusion currents, the rates of *chemically independent* reactions are mutually dependent. This so called *coupling by diffusion* implies that: *The rate of metabolism of a given substrate is influenced by the rates of metabolism of metabolically unrelated substrates.* Furthermore, the presence, in the medium, of an *inert* solute to which the membrane is permeable will influence the rates of concentration–dependent reactions in the cell. The spatial distribution of a catalyst in the diffusion field within the cell is examined. The general effect of including heat flow and thermal diffusion in the cellular diffusion problems is briefly pointed out.

Introduction. It is well known that when two or more irreversible transport processes (e.g. heat conduction, electrical conduction, diffusion) take place in a given system there is mutual interaction among the individual transports. Not only do the individual processes interfere with one another but in general they may not occur separately; i.e. one such process obligatorily entails the others. Various combinations of such "coupled" transports constitute familiar phenomena.

An imposed electromotive force in a conductor of dissimilar metals causes the evolution (or absorption) of heat at the junctions (Peltier effect); the converse is the "thermoelectric force." An imposed electromotive force in an electrolytic solution causes the transport of matter; the converse is the electromotive force of a concentration cell. A solution in which there exists a gradient in temperature exhibits also a gradient in composition. This phenomenon first studied by Soret is known as the "Soret effect." The flow of matter due to a thermal gradient is called thermal diffusion; the converse

effect is less well known but has been qualitatively demonstrated (references cited in Onsager, 1931a).

The above are examples of the mutual dependence of the transport of heat and electricity, matter and electricity, heat and matter. Usually the individual "flows" or "currents" are taken, in the absence of interaction, to be given by empirical laws; viz., Fourier's Law, Ohm's Law and Fick's Law. When interaction is not to be neglected the currents are taken to be given by phenomenological relations which express any current as a linear combination of all of the gradients. For example for the current of diffusion, $\vec{J}$, and of heat flow, $\vec{q}$, the equations

$$\vec{J} = -(D\nabla C + D_T \nabla T);$$

$$\vec{q} = -(k\nabla T + k_C \nabla C)$$

express the assumptions that a temperature gradient produces a flow of matter and that a concentration gradient produces a flow of heat. The coefficients D, D_T and k are the diffusion, thermal diffusion and thermal conductivity coefficients respectively; C is the concentration and T the absolute temperature. Relations analogous to the above but expressed in terms of the "forces" which produce the currents, viz. $\nabla\mu$ and $\nabla(1/T)$ where μ is the chemical potential, are more often used (Onsager, 1931a & b; Eckart, 1940; Leaf, 1946). When one considers multi-constituent solutions, there must be added to the above examples the mutual interaction among the transports of solutes (Onsager, 1931a).

Onsager's Generalization of Fick's Law.

The chief effect of the forces of interaction is of a thermodynamic nature: The force of diffusion, $-\nabla\mu$, is different (usually less) from that which would obtain, under the same concentration gradient, in an ideal solution. Also the velocity of diffusion in a non-ideal solution is, due to electrostatic and "hydrodynamic" interaction, for a given force $-\nabla\mu$ different from that in an ideal solution. The generalization of Fick's Law (Onsager and Fuoss, 1932; Onsager, 1945) for a solution of s solutes relates the velocities of diffusion v_i (relative to the solvent) linearly to the "forces" or potential* gradients $-\nabla\mu_i$:

*When electrolytes are involved the μ_i are the electrochemical potentials, otherwise μ_i denotes the chemical potential, equation (6), of Gibbs.

$$\vec{J}_i \equiv \vec{v}_i C_i = -\sum_{j=1}^{s} \Omega_{ij} \nabla \mu_j , \quad i = 1, 2, \cdots s . \tag{1}$$

The solvent is assumed to be the dominant constituent; this is certainly unambiguous when dilute aqueous solutions are being considered. The flow of any solute is defined relative to a local coordinate frame moving with the solvent. Bulk motion (cf. also Eckart, 1940) determined by hydrodynamic considerations may also be imposed. One may in practice assume either that the velocity of the solvent or that the "bulk velocity" (Onsager and Fuoss, 1932),

$$\vec{\bar{v}} = \sum_i \vec{J}_i \tilde{V}_i , \tag{2}$$

where $\tilde{V}_i$ is the partial molal volume of the ith solute, obeys the hydrodynamic equation. The omission of the thermal diffusion term from equation (1) amounts to the assumption of an isothermal system in which there are gradients in composition and requires some comment, but this is deferred until later.

The relations $\Omega_{ij} = \Omega_{ji}$ hold for all j and i; they state that the flow of solute i caused by a unit force on solute j is equal to the flow of j due to a unit force on i. These symmetry relations, which seem physically necessary for the interaction expressed by (1), are implicit in the "principle of least dissipation of energy" (Onsager, 1931a & b; Onsager and Fuoss, 1932) and are derivable on the basis of the principle of microscopic reversibility (Onsager, 1931a & b; Casimir, 1945).

The form of the simple Fick's Law for a two component solution analogous to equation (1) is

$$\vec{J} = \vec{v}\, C = -\Omega \nabla \mu , \tag{3}$$

from which it is seen that Ω has the physical significance that Ω/C is the "mobility" or the velocity caused by a unit force $-\nabla\mu$; the quantity C/Ω is the "frictional coefficient" [cf. Hearon, 1950b, equation (39), etc. and equation (8) below]. Comparison of (3) with the usual form

$$\vec{J} = -D \nabla C \tag{4}$$

shows that

$$D = \Omega \frac{\partial \mu}{\partial C} . \tag{5}$$

If μ is given by

$$\mu = \mu^0 + R\,T \ln \gamma\, C\,, \tag{6}$$

where γ is the activity coefficient, equation (5) gives

$$\Omega/C = D/\,R\,T\left(1 + \frac{\partial \ln \gamma}{\partial \ln C}\right)\,. \tag{7}$$

For an ideal solution ($\gamma \equiv 1$), (7) becomes

$$\Omega/C = D/RT\,. \tag{8}$$

It is of some interest to compare the remarks following (3) and equation (8) to the results obtained by G. Young (1938, pp. 171-172) from the Stokes-Navier equations and to those of N. Rashevsky (1949).

In an ideal solution in which the solutes diffuse independently equation (1) reduces to

$$\vec{J}_i = -\,\Omega_{ii} \nabla \mu_i\,. \tag{9}$$

If departure from ideality is due to compound-formation, one diffusing substance carries another with it thereby influencing its flow and there will be coefficients Ω_{ij}, $i \neq j$, which are not zero. On the basis of this physical picture the simple law (9) would hold for each compound and molecular species actually present in the system (Lamm, 1947). It is not always possible to satisfactorily describe departure from ideality in terms of compound-formation and the phenomenological description (1), albeit non-committal, is employed. Alternatively, if possible, the forces of interaction may be specified. Greatest progress along these lines has been made for the case of electrolytes, and Onsager and Fuoss (1932, p. 2761) give expressions for the order of magnitudes of the Ω_{ij}. Expressions for the forces of interaction and "drag forces" are also available for the imperfect gas (cf. Young, 1938 and references therein; Landahl, 1942).

While the form (1) is perhaps most useful for certain formal discussion we will find the alternative form,

$$\vec{J}_k = -\sum_j D_{kj} \nabla C_j\,, \quad k = 1, 2, \cdots s\,, \tag{10}$$

given by Onsager (1945), of greatest utility. He has presented relations among the D_{kj} derived from equating the bulk velocity (2) to zero. A discussion of equation (10) similar to that presented for equation (1) can be given; relations between the Ω_{kj} and the D_{kj} can

be derived (Eckart, 1940; Onsager, 1945). We will refer to the D_{kj}, $j \neq k$, as the "drag coefficients" or "cross coefficients."

Purpose of the Paper.

It is the purpose of this paper to present the solution of several problems in which the currents, $\vec{J}_k$, are taken from equation (10). Since some of these problems have been previously solved (Rashevsky, 1948) under the assumption of the simple Fick's Law, equation (4), it will be the purpose here to point out differences and new features introduced by retaining the cross-coefficients D_{kj}, $k \neq j$. It will be seen that the formal boundary value problem presented by even the simplest case is considerably different when the generalized Fick's Law is used. Further, it becomes necessary to introduce generalized permeability expressions and cross-permeability coefficients, h_{kj}, analogous to the D_{kj}.

The situation arises as a consequence of (10), wherein it is possible to have a stationary, non-equilibrium distribution of an inert solute in which the concentration is greater (or less) in the cell than in the environment. The disparity between the cellular and environmental concentration is determined by the rates of metabolism of whatever metabolites are being produced or consumed in the cell; a change in the rates of metabolism can cause inert solute to flow against a concentration gradient. This has been discussed briefly elsewhere (Hearon, 1950b) from the standpoint of thermodynamics, and the details of the diffusion problem are herein supplied.

It can be seen readily from the results to follow that a consequence of equation (10) is, since the spatial concentration distribution of a given solute is determined by the distribution of all other solutes, that the rate of one chemical reaction may be influenced by another of which it is quite independent *chemically*. This mutual dependence of *chemically independent* rates is called "coupling by diffusion."

Since in general the solutions of the diffusion equation are tractable only when certain spatial symmetry can be assumed and, more especially, when stringently simplifying expressions are employed for the chemical rates of production and consumption, no very general treatment can be given. Considerable abstraction is necessary and, in fact, some *physical* approximation must be made. However, the salient features can be seen from the highly simplified (not very realistic) cases treated and certain qualitative generalizations are apparent. There are special and limiting cases of the problems dis-

cussed which are not investigated in detail but which are of interest for further study.

The influence of the cross-coefficients upon the transient or time-dependent solutions is perhaps more interesting, and from the experimental point of view more important, than the steady state situations discussed here. Only the most simple variable state cases are briefly discussed in a subsequent note.

The equation of continuity.

By the superscript i we will denote quantities which refer to the interior of the cell and by the superscript e quantities referable to the environment. The equation of continuity for the kth substance inside of the cell is, in the steady state,

$$-\nabla \cdot \vec{J}_k{}^i + q_k = 0, \quad k = 1, 2, \cdots s, \tag{11}$$

where the $\vec{J}_k{}^i$ are obtained from (10) by inserting the values $D_{kj}{}^i$ and $C_j{}^i$. Here the first physical approximation appears: We are neglecting thermal diffusion and the "inverse Soret effect" and assuming an isothermal system. This is discussed in a later section. The rate, q_k, of production per unit volume of the kth substance may depend upon any, all or none of the $C_j{}^i$ and is negative when the substance is consumed. Since $q_k = 0$, for all k, in the environment the equation of continuity outside of the cell is

$$-\nabla \cdot \vec{J}_k{}^e = 0, \quad k = 1, 2, \cdots s. \tag{12}$$

Substitution of $\vec{J}_k{}^i$ from (10) into (11) gives

$$\sum_j D_{kj}{}^i \nabla^2 C_j{}^i + \sum_j \nabla D_{kj}{}^i \cdot \nabla C_j{}^i + q_k = 0, \quad k = 1, 2, \cdots s. \tag{13}$$

The second physical approximation which we will make, and which is a composite one, is to neglect the second summation in (13). This amounts to assuming that the $D_{kj}{}^i$ are: 1) inherently independent of the space coordinates and 2) independent of the $C_j{}^i$. If the $D_{kj}{}^i$ depend upon the space coordinates only by virtue of their dependency upon the $C_j{}^i$, the second summation in (13) is

$$\sum_i \sum_j \frac{\partial D_{kj}{}^i}{\partial C_l{}^i} \nabla C_l{}^i \cdot \nabla C_j{}^i. \tag{14}$$

For a closed system in which $q_k = 0$, *for all* k, it is possible to neg-

lect (14) if the initial conditions are that every ∇C_k^i is small, for the gradients continually decrease, and if (14) were initially negligible it may be neglected throughout the course of the diffusion process. This is the familiar proposition of differential diffusion (Harned, 1947). Of course in such a case the only steady state solutions are $C_k^i = C_{k0}^i = \text{const.}$ for all k. When every q_k is different from zero, then, quite regardless of initial conditions, there are steady state solutions in which the ∇C_j^i may be by no means small. In fact, as will appear in the next section, the vanishing of a *particular* q_k does not even insure that the *corresponding* gradient, ∇C_k, is small. Furthermore in most cellular problems the angle between the vectors ∇C_l^i and ∇C_j^i will be, for all l and k, zero or π. Therefore in neglecting (14) we must do so on the basis that $\partial D_{kj}^i / \partial C_l^i$ is negligibly small and not on the assumption that the scalar products $\nabla C_l^i \cdot \nabla C_j^i$ are small. By assuming, in writing (14), that the D_{kj}^i are functions of the C_j^i alone we have also assumed that the interior of the cell is a homogeneous structure. This is a virtually necessary, but not particularly good, assumption.

With the above approximations, which are not so readily justified here as in some experimental *in vitro* setups, we take the equation of continuity to be

$$\sum_j D_{kj}^i \nabla^2 C_j^i + q_k = 0, \quad k = 1, 2, \cdots s \tag{15}$$

inside of the cell and

$$\sum_j D_{kj}^e \nabla^2 C_j^e = 0, \quad k = 1, 2, \cdots s \tag{16}$$

in the environment. Unlike the situation when the simple Fick's Law is employed, the members of the set (15) are not independent, whatever the dependency of the q_k upon the C_k^i.

Spherical cell; q_k constant.

Consider a cell which is producing s substances at the constant rates q_k, $k = 1, 2 \cdots s$. It is assumed that the q_k are independent. Under these conditions of constant q_k the set (15) may be reduced to s independent equations; each equation is still of second order. The solutions of (15) are the solutions of

$$\left.\begin{aligned} &\nabla^2 C_k^i = -Q_k^i, \\ &\qquad\qquad k = 1, 2, \cdots s \\ &Q_k^i \equiv \sum_j q_j R_{kj}, \end{aligned}\right\} \tag{17}$$

where R_{kj} is the reduced cofactor of the element $D_{jk}{}^{i}$ of the determinant $|D_{kj}{}^{i}|$. Similarly the set (16) becomes

$$\nabla^2 C_k{}^{e} = 0, \quad k = 1, 2 \cdots s, \tag{18}$$

and there are no other solutions, for in general the determinant $|D_{kj}{}^{e}|$ is different from zero.

The boundary conditions are

$$\vec{n} \cdot \vec{J}_k{}^{i} = \vec{J}_k{}^{e} \cdot \vec{n}, \text{ on } \sigma; \quad k = 1, 2 \cdots s, \tag{19}$$

where σ is the cell surface and $\vec{n}$ is a unit vector with the direction of the outward normal to σ;

$$\vec{n} \cdot \vec{J}_k{}^{i}(\sigma) = \Gamma_k, \quad k = 1, 2 \cdots s, \tag{20}$$

where Γ_k is the flow of the kth substance across the cell membrane and

$$C_k{}^{e} \to C_k{}^{0}, \quad \text{as} \quad r \to \infty. \tag{21}$$

For the special case of the spherical cell

$$\nabla^2 C_k{}^{i} = \frac{1}{r} \frac{\partial^2 (r C_k{}^{i})}{\partial r^2}, \tag{22}$$

and the solutions of equations (17) are

$$C_k{}^{i} = -\frac{Q_k{}^{i}}{6} r^2 + A_k, \quad r \leq r_0, \quad k = 1, 2, \cdots s, \tag{23}$$

where the A_k are constants of integration and r_0 is the radius of the cell. We have used the condition that $C_k{}^{i}$ be finite at $r = 0$ to eliminate s of the constants which appear in the integrals of (17). The solutions of (18) are

$$C_k{}^{e} = C_k{}^{0} + B_k/r, \quad r \geq r_0, \quad k = 1, 2 \cdots s, \tag{24}$$

where the B_k are constants of integration and we have used condition (21).

The boundary conditions (19), with (23), (24) and (10), give

$$\left.\begin{aligned} \sum_j D_{kj}{}^{e} B_j &= \frac{r_0^3}{3} \sum_j D_{kj}{}^{i} Q_j{}^{i} \\ &= \frac{r_0^3}{3} q_k, \quad k = 1, 2 \cdots s, \end{aligned}\right\} \tag{25}$$

which set determines the B_k as

$$B_k = \frac{r_0^3}{3} \sum_j q_j L_{kj} \equiv \frac{r_0^3}{3} Q_k^e , \qquad (26)$$

where L_{kj} is the reduced cofactor of the element D_{jk}^e in the determinant $|D_{kj}^e|$; Q_k^e is the same function of the D_{kj}^e that Q_k^i is of the D_{kj}^i.

The proof of the last equality in (25) is as follows: From the definition of Q_j it follows that

$$\sum_j D_{kj}^i Q_j^i = \sum_j \sum_n D_{kj}^i R_{jn} q_n = \sum_n q_n \delta_{n,k} , \qquad (27)$$

where $\delta_{n,k}$ is the Kronecker delta. The term with $n = k$ is

$$q_k \sum_j D_{kj}^i R_{jk} = q_k \sum_j D_{jk}^i R_{kj} = q_k , \quad k = 1, 2 \cdots s , \qquad (28)$$

because the summations in (28) are the expansions of the determinant $|D_{kj}^i|$ by elements of the kth row or column, divided by the de terminant. The terms with $n \neq k$ are

$$q_n \sum_j D_{kj}^i R_{jn} = 0 , \qquad \begin{matrix} k = 1, 2, \cdots, \neq n \\ n = 1, 2, \cdots, \neq k \end{matrix} \qquad (29)$$

since the terms in these summations are the products of the reduced cofactors of the nth row and the elements of the kth row. By known properties of determinants (Aitken, 1948), expansions in terms of alien cofactors vanish identically.

The imposition of conditions (20) requires some discussion: The natural and straightforward generalization, which is consistent with (10), of the conventional permeability expression requires that equations (20) read

$$-\sum_j D_{kj}^i \left(\frac{\partial C_j^i}{\partial r} \right)_{r=r_0} = \sum_j h_{kj} (C_j^i - C_j^e)_{r=r_0} , \quad k = 1, 2 \cdots s. \qquad (30)$$

The right hand-side of equation (30) is Γ_k, the flow across the membrane in the positive r-direction of the kth substance; the h_{kj}, $k \neq j$, are the "cross permeability coefficients." The above form of Γ_k does *not* imply any particular mechanism of permeation. It expresses the assumption that if the flows, $\vec{J}_k^i$ (σ), *to* the membrane are mutually dependent, then the flows *across* the membrane also are, and in the same manner. In the simple case the flows through the membrane are proportional to the concentration differences across the membrane; in the generalized case the flows across the membrane

are linear combinations of the concentration differences. This appears to be a necessary assumption, *whatever* the physical basis of permeation, whenever equation (10) is assumed to hold rather than equation (4). If it is assumed that the membrane is a distinct "bulk phase" then

$$\Gamma_k = -\sum_j D_{kj}{}^m \left(\frac{\partial C_j}{\partial r} \right)_m = \sum_j K_j D_{kj}{}^m \frac{(C_j{}^i - C_j{}^e)_{r=r_0}}{\delta}, \qquad (31)$$

where the D_{kjm} are the coefficients in the membrane, $(\partial C_j/\partial r)m$ the gradients in the membrane, K_j the partition coefficients between the environment and membrane substance and δ the thickness of the membrane. The generalized permeability coefficients are then

$$h_{kj} \equiv K_j D_{kj}{}^m/\delta . \qquad (32)$$

In (30) and (31) it has been assumed that the partition coefficients, α_j, between the environment and cell substance are unity. This restriction is easily removed. Needless to state, there is some doubt to be raised with regard to considering the membrane [probably $\delta < 10m\mu$ (Danielli, 1942)] as a "bulk phase." It is interesting to note that in the "stationary film" theory of the kinetics of gaseous absorption into liquid phases, films of the order of 10^{-4} cm. (Roughton, 1941; Davis and Crandall, 1930) have been regarded as "bulk matter" with good agreement between theory and experiment.

With equations (23), (24) and (26), equations (30) give

$$\left.\begin{aligned} \sum_j h_{kj} A_j &= \frac{r_0}{3} \sum_j D_{kj}{}^i Q_j{}^i + \sum_j h_{kj} p_j , \\ p_j &\equiv \frac{r_0{}^2}{6} Q_j{}^i + \frac{r_0{}^3}{3} Q_j{}^e + C_j{}^0 . \end{aligned}\right\} \qquad (33)$$

Using the result (27), the solutions of equations (33) may be written as

$$A_k = \frac{r_0}{3} \sum_j q_j H_{kj} + \sum_j \sum_n h_{jn} p_n H_{kj} , \qquad (34)$$

where H_{kj} is the reduced cofactor of the element h_{jk} in the determinant $|h_{kj}|$. By the same argument, equations (28) and (29), by which (27) was established, it follows that

$$\sum_n p_n \sum_j h_{jn} H_{kj} = \sum_n p_n \delta_{k,n} . \qquad (35)$$

Therefore, with p_k from the definition in (33), equations (34) give

$$A_k = C_k^0 + \frac{r_0}{3} Q_k^m + \frac{r_0^2}{6} Q_k^i + \frac{r_0^2}{3} Q_k^e, \quad k = 1, 2, \cdots s, \tag{36}$$

where

$$Q_k^m \equiv \sum_j q_j H_{kj}, \quad k = 1, 2, \cdots s \tag{37}$$

may be formed from Q_k^i by replacing D_{kj}^i by h_{kj}.

If in equations (30) the terms in Γ_k are taken as

$$h_{kj} (C_j^i - \alpha_j C_j^e)_{r=r_0},$$

then in (36) C_k^0 is replaced by $\alpha_k C_k^0$ and $\frac{r_0^2}{3} Q_k^e$ is replaced by $\alpha_k \frac{r_0^2}{3} Q_k^e$.

This completes the solution of the problem with the final results:

$$C_k^i = C_k^0 + \frac{r_0}{3} Q_k^m + \frac{Q_k^i}{6} (r_0^2 - r^2) + \frac{r_0^2}{3} Q_k^e, \quad k = 1, 2 \cdots s; \tag{38}$$

$$C_k^e = C_k^0 + \frac{r_0^3}{3} Q_k^e \frac{1}{r}, \quad k = 1, 2, \cdots s. \tag{39}$$

The solutions of the same problem under the assumption of the simple Fick's Law are

$$C_k^i = C_k^0 + \frac{r_0}{3} \frac{q_k}{h_{kk}} + \frac{q_k}{6 D_{kk}^i} (r_0^2 - r^2) + \frac{r_0^2}{3} \frac{q_k}{D_{kk}^e}; \tag{40}$$

$$C_k^e = C_k^0 + \frac{r_0^3}{3} \frac{q_k}{D_{kk}^e} \frac{1}{r}. \tag{41}$$

We will refer to this as the *simple case* as opposed to the *generalized case* (38) and (39). The simple and generalized cases may be compared as follows:

1) In the simple case the parameters in C_k^i and C_k^e are determined by the properties of the kth solute alone. In the generalized case these parameters are determined by the properties of all of the solutes present.

2) In both cases the C_k^i may be separated into terms contributed by the membrane, internal diffusion properties and external diffusion properties. The simple constants h_{kk}, D_{kk}^i and D_{kk}^e are replaced in the generalized case by the corresponding determinants $|h_{kj}|$, $|D_{kj}^i|$ and $|D_{kj}^e|$; the q_k are replaced by the appropriate determinants from (17), (26) and (37). The characterization of the membrane properties by the set h_{kj} is formally similar to the situation discussed by M. F. Morales (1944). In the Morales' case the mutual dependence of the diffusion currents is based upon a physical situation somewhat different from that implied by equation (10). It is worth mentioning that if equation (32) is accepted, then Q_k^m, from (37), is proportional to the membrane thickness δ. Thus in problems (Rashevsky, 1948, p. 108) in which it is necessary to invoke explicitly the dependence of permeability upon δ, the same formal relations may be preserved in the generalized case.

3) In the simple case $C_k^i(r)$ is a parabola with apex at the cell center open downward if $q_k > 0$; open upward if $q_k < 0$: it is a constant, (C_k^0 if $\alpha_k = 1$), if $q_k = 0$. The differences $C_k^i(0) - C_k^i(r_0) = q_k r_0^2/6D_{kk}^i$ and $C_k^i(r_0) - C_k^e(r_0) = q_k r_0/3h_{kk}$, $\alpha_k = 1$, are directly proportional to and have the sign of q_k. Thus in the simple case the concentration of a produced solute always increases toward the cell center and is always higher everywhere in the cell than in the environment and conversely for a consumed solute; the concentration of an inert, $q_k = 0$, solute has a constant value in the cell and environment.

In the generalized case $C_k^i(r)$ is a maximum or a minimum at $r = 0$ when $Q_k^i > 0$ or when $Q_k^i < 0$ respectively. The differences $C_k^i(0) - C_k^i(r_0) = Q_k^i r_0^2/6$ and $C_k^i(r_0) - C_k^e(r_0) = Q_k^m r_0/3$ are linear in q_k and have the sign of Q_k^i and Q_k^m respectively. Thus in this case the concentration of a *produced* solute or of a *consumed* solute may increase *or* decrease toward the cell center and it may be that $C_k^i(r_0) < C_k^e(r_0)$ or that $C_k^i(r_0) > C_k^e(r_0)$; further, depending upon the sign of Q_k^e, C_k^e may increase or decrease toward $r = \infty$: *Similar statements apply to an inert solute* ($q_k = 0$). The vanishing of q_k does not then insure a zero gradient nor are the signs of the slopes of $C_k^i(r)$ and $C_k^e(r)$ determined directly by the sign of q_k as in the simple case. These points have been discussed elsewhere (Hearon, 1950b) for the special case $s = 2$, $q_1 = 0$, $q_2 < 0$.

When $Q_k^i = 0$, C_k^i has a constant value in general different from C_k^0 even if $\alpha_k = 1$. Such a situation would *simulate*, under the assumption of the simple Fick's Law, a substance for which $q_k = 0$

or $D_{kk}{}^{i} = \infty$. Similarly $C_k{}^{e} = C_k{}^{0}$ if $Q_k{}^{e} = 0$ and $C_k{}^{i}(r_0) = C_k{}^{e}(r_0)$ if $Q_k{}^{m} = 0$. The difference between the *mean* cellular concentration, $\bar{C}_k{}^{i} = \frac{1}{V}\int_V C_k{}^{i} dV$, and $C_k{}^{0}$, the unperturbed external concentration,

$$\bar{C}_k{}^{i} = C_k{}^{0} + \frac{r_0}{3} Q_k{}^{m} + \frac{r_0{}^{2}}{15} Q_k{}^{i} + \frac{r_0{}^{2}}{3} Q_k{}^{e} \tag{42}$$

is the quantity most likely determined experimentally. This quantity is positive or negative depending upon the relative values of $Q_k{}^{i}$, $Q_k{}^{m}$ and $Q_k{}^{e}$ subject to the restriction on $C_k{}^{0}$ that

$$A_k > 0\,, \tag{43}$$

which insures $C_k{}^{i} > 0$ for $0 \leq r \leq r_0$, which we have assumed throughout. It is *probable* that $Q_k{}^{i}$, $Q_k{}^{e}$ and $Q_k{}^{m}$ will have like signs (for the values of the D_{kj}, $j \neq k$ are not unrelated to those of the D_{kk}), but this is not a necessity except in special circumstances [e.g. the special case already treated (Hearon, 1950b)].

4) The direction of the currents $\vec{J}_k{}^{i}$ and $\vec{J}_k{}^{e}$ are *in both cases* determined by the sign of q_k, for in both cases the currents are

$$\vec{J}_k{}^{i} = \frac{q_k}{3}\vec{r}\,; \tag{44}$$

$$\vec{J}_k{}^{e} = \frac{q_k}{3} r_0{}^{3} \frac{\vec{r}}{r^3}. \tag{45}$$

These relations are obvious for the simple case. For the generalized case equation (44) follows from equations (10), (23) and (27); equation (45) from equations (10), (24) and (25). In both cases then the *currents* vanish with q_k. In the generalized case the *gradients* $\nabla C_k{}^{i}$ and $\nabla C_k{}^{e}$ have directions determined by the signs of $Q_k{}^{i}$ and $Q_k{}^{e}$ and *do not* vanish with q_k. In fact if the signs of q_k and $Q_k{}^{i}$ are different, then $\vec{J}_k{}^{i}$ and $\nabla C_k{}^{i}$ are oppositely directed and the solute flows opposite to its *own* gradient. There are however thermodynamic restrictions upon this situation: The quadratic form

$$\left.\begin{aligned} \left(\frac{r}{3}\right)^2 \sum_k q_k \frac{Q_k{}^{i}}{C_k{}^{i}} &= \left(\frac{r}{3}\right)^2 \sum_k \sum_j q_k\, q_j \frac{R_{kj}}{C_k{}^{i}} \\ &= \sum_k \sum_j M_{kj}\, \vec{J}_k{}^{i} \cdot \vec{J}_j{}^{i}\,, \\ M_{kj} &\equiv R_{kj}/C_k{}^{i} \end{aligned}\right\} \tag{46}$$

must be positive definite. For if equations (10) be solved for the ∇C_k there results

$$\nabla C_k{}^i = -\sum_j R_{kj} \vec{J}_j{}^i . \tag{47}$$

Observing (44) it is seen that (46) is

$$-\frac{1}{RT}\left(\frac{dF}{dt}\right)_{\text{diff.}} = -\frac{1}{RT}\sum_j \nabla \mu_j \cdot \vec{J}_j{}^i \geq 0 \tag{48}$$

[cf. Hearon, 1950b, equation (35)], where F is the Gibbs free energy per unit volume. The matrix $[M_{kj}]$ is, excepting the scalar multiplier RT, the reciprocal of the matrix $[\Omega_{kj}]$ as is seen by comparing (47) with the solution of (1) for $\nabla \mu_k$ and taking $\mu = \mu^0 + RT \ln C_k$. Similarly, by solving equations (1) for ∇C_k it is seen that the matrix $[R_{kj}]$ is the reciprocal of the matrix $[\Omega_{kj}/C_j{}^i]RT$. Except for a scalar factor then, (46) is the *dissipation function* of Onsager (1931a, 1932, 1945). The requirement that this be positive definite imposes inequality restrictions upon the $D_{kj}{}^i$ (Onsager, 1931a; Eckart, 1940; Meixner, 1942).

Equations (17) and (18) and the boundary conditions (19)–(21) are independent of the coordinate system appropriate to the problem at hand. Thus in the integrals of (17) in any coordinate system (e.g. Young, 1939), obtained under the assumption of (4) and q_k constant, one may replace $q_k/D_{kk}{}^i$ everywhere by $Q_k{}^i$ and obtain the generalized case. The subsequent imposition of (19)–(21) is conceivably a difficult problem in general.

It will sometimes, but not often, happen that certain members of the set (17) are integrable by quadratures when one or more of the q_k depend upon $C_j{}^i$. We will in fact later discuss one such case.

Spherical Cell; $q_k = \sum_j k_{kj} C_j{}^i$.

When the q_k are linear combinations of the $C_j{}^i$, the set (15) can be solved, although if $s > 2$ difficulty of an algebraic nature arises, viz., the solution of an algebraic equation of degree $> 2s$. When the q_k are proportional to a concentration the situation is, of course, simpler but even with $s = 2$ there is considerable algebraic tedium associated with the boundary conditions and the results cannot be simply and concisely contrasted to the simple case.

We wish to point out for the simple case $s = 2$, $q_1 = k_1 C_1{}^i$, $q_2 = k_2 C_2{}^i$ the dependence of the *form* of the solutions upon the

physical situation. The set (15) is written, using (22), as

$$\sum_j D_{kj}{}^i \mathcal{D}^2 X_j + k_k X_k = 0, \quad k = 1, 2, \tag{49}$$

where

$$\left.\begin{aligned} X_k &\equiv r C_k{}^i, \\ \mathcal{D} &\equiv \frac{d}{dr}. \end{aligned}\right\} \tag{50}$$

The roots of the auxiliary equation are

$$\lambda^2 = \frac{-a \pm \sqrt{a^2 - 4 k_1 k_2 \Delta}}{2\Delta} = \alpha^2, \beta^2, \tag{51}$$

where $a = k_2 D_{11}{}^i + k_1 D_{22}{}^i$, $\Delta \equiv |D_{kj}{}^i|$ and α is associated with the positive sign in (51). Now it will be recalled (Rashevsky, 1948) that in the corresponding simple case ($D_{12}{}^i = D_{21}{}^i = 0$) for a *produced* solute $X_j = A_j \sin \alpha r$ and for a *consumed* solute $X_j = A_j \sinh \alpha r$. In the more general case X_j has a variety of forms for the roots (51) may be all real, all pure imaginary, two real and two pure imaginary or all complex. For brevity these cases are tabulated below in Table I giving the form of X_k after the elimination, by the condition $C_k{}^i =$ finite at $r = 0$, of extraneous constants. It is assumed throughout that $\Delta > 0$. The constants g_{k1}, g_{k2}, g_{k3} are not independent. When both substances are produced, or both are consumed, the form of X_k is similar to that in the simple case, provided that $a^2 > 4k_1k_2\Delta$, but *two* discrete sin or sinh terms appear. When $a^2 < 4k_1k_2\Delta$, which can occur only if k_1 and k_2 have like signs, the form 5 holds whether the substances are produced *or* consumed. For the special case $a^2 = 4k_1k_2\Delta$ the sin appears if the substances are produced; the sinh if they are consumed, but these terms are multiplied by a term linear in r. If one substance is produced and one is consumed, the form 6 holds for *both* substances. The special case $a = 0$ is presented because of the relation of the roots in this case to those in 3 and 4: The form is not distinct from that when $a \neq 0$. Cases 8 and 9 give the distribution of an inert solute in the diffusion field of a consumed and produced substance respectively. The immediate effect of the inert solute upon the metabolized one is to increase β since $k_2 D_{11}{}^i/\Delta > k_2 D_{22}{}^i$ but the values of g_2 in these cases will be different also from those in the corresponding simple case.

TABLE I

	Constants	Roots	$X_k = r\,C_k^{\,i}$
1.	$k_1, k_2 > 0$, discriminant > 0	$\pm i\,\alpha$ $\pm i\,\beta$	$g_{k1} \sin \alpha r + g_{k2} \sin \beta r$
2.	$k_1, k_2 < 0$, discriminant > 0	$\pm \alpha$ $\pm \beta$	$g_{k1} \sinh \alpha r + g_{k2} \sinh \beta r$
3.	$k_1, k_2 > 0$, discriminant $= 0$	$\pm i\sqrt[4]{k_1 k_2/\Delta}$ $\pm i\sqrt[4]{k_1 k_2/\Delta}$	$(g_{k1} + g_{k2} r) \sin \alpha r + g_{k3} r \cos \alpha r$
4.	$k_1, k_2 < 0$ discriminant $= 0$	$\pm \sqrt[4]{k_1 k_2/\Delta}$ $\pm \sqrt[4]{k_1 k_2/\Delta}$	$(g_{k1} + g_{k2} r) \sinh \alpha r + g_{k3} r \cosh \alpha r$
5.	$k_1, k_2 \lesseqgtr 0$ discriminant < 0	$a_1 \pm i\,b_1$ $a_2 \pm i\,b_2$	$g_k(e^{a_1 r} \sin b_1 r + e^{a_2 r} \sin b_2 r)$
6.	$k_1 \lesseqgtr 0, k_2 \gtreqless 0$, $a \neq 0$	$\pm \alpha$ $\pm i\,\beta$	$g_{k1} \sinh \alpha r + g_{k2} \sin \beta r$
7.	$k_1 \lesseqgtr 0, k_2 \gtreqless 0$, $a = 0$	$\pm \sqrt[4]{-k_1 k_2/\Delta}$ $\pm i\sqrt[4]{-k_1 k_2/\Delta}$	$g_{k1} \sinh \alpha r + g_{k2} \sin \beta r$
8.	$k_1 = 0$,	$\pm \alpha = 0$	$X_2 = g_2 \sin \beta r$
	$k_2 > 0$	$\pm \sqrt{\dfrac{-k_2 D_{11}^{\,i}}{\Delta}} = \pm i\,\beta$	$X_1 = g_{11} \sin \beta r + g_{12} r$
9.	$k_1 = 0$,	$\pm \alpha = 0$	$X_2 = g_2 \sinh \beta r$
	$k_2 < 0$	$\pm \sqrt{\dfrac{-k_2 D_{11}^{\,i}}{\Delta}} = \pm \beta$	$X_1 = g_{11} \sinh \beta r + g_{12} r$

Coupling by Diffusion.

It can be seen from the above results that the rates of *chemically* independent reactions are mutually dependent. The rate of a given reaction is dependent upon the occurrence and magnitude of the rates of other reactions which are proceeding, but with which it has no products or reactants in common. Furthermore, from cases 8 and 9 above it is seen that an *inert* substance may influence the rate of metabolism of a given solute. It has already been seen that the effect of the drag coefficients in such a case is to increase β, (cases 8 and 9), but also the constant g_2 will be determined in part by the unperturbed external concentration $C_2^{\,e}$. Therefore the rate of metabolism of "substance 1" will be influenced by the cross coefficients D_{12} and D_{21} and the external concentration of the inert "substance 2."

A detailed assessment of such effects requires evaluation of the constants g_{kj} in cases 1–9 and some concept of the magnitudes of the D_{kj}, $k \neq j$. We wish to exhibit a simple case in which the phenomenon of coupling by diffusion is particularly transparent from even the partially solved boundary value problem.

Consider the case: $s = 2$, $q_1 = \text{const.}$, $q_2 = -k_2 C_2$, $k_2 > 0$. In these circumstances $\nabla^2 C_2{}^i$ from (17) is directly integrable and substitution of $C_2{}^i(r)$ into $\nabla^2 C_1{}^i$ from (17) gives an equation integrable by successive quadratures. The results are, after requiring that $X_k = 0$, at $r = 0$:

$$C_1{}^i = -\frac{D_{12}{}^i}{D_{11}{}^i} A_2 \frac{\sinh \alpha r}{r} - \frac{q_1 r^2}{6 D_{11}{}^i} - \frac{D_{12}{}^i D_{21}{}^i}{D_{11}{}^i D_{11}{}^i} \frac{q_1}{k_2} + A_1; \tag{52}$$

$$C_2{}^i = A_2 \frac{\sinh \alpha r}{r} + \frac{D_{21}{}^i q_1}{D_{11}{}^i k_2}, \tag{53}$$

where $\alpha = \sqrt{\dfrac{k_2 D_{11}{}^i}{\Delta}}$. If $q_2 = k_2 C_2{}^i$, $k_2 > 0$ then in (52) and (53) sinh is replaced by sin. The terms in $C_1{}^i$ contributed by substance 2 vanish with $D_{12}{}^i$, the "drag of 2 on 1." When $D_{12}{}^i = D_{21}{}^i = 0$, (52) reverts to the simple form (40). The additive contribution in (53) from substance 1 is proportional to $D_{21}{}^i$ and to q_1. The *additive* contribution of substance 1 to the *total* rate of consumption of substance 2, $4 \pi r_0{}^3 D_{21}{}^i q_1/3 D_{11}{}^i$, may be appreciable if q_1 is sufficiently large. If it is assumed that $h_{2j} = \infty$, which is no essential restriction, the condition (20) becomes for $k = 2$,

$$C_2{}^i = C_2{}^e \quad \text{at} \quad r = r_0. \tag{54}$$

If conditions (19) are replaced by

$$\int_V q_k \, dV = \int_\sigma \vec{J}_k{}^e \cdot \vec{d\sigma}; \qquad k = 1, 2, \tag{55}$$

the quantity A_2 may be evaluated rather directly giving

$$A_2 = \frac{-q_1 \left\{ \dfrac{V D_{21}{}^i D_{11}{}^e}{D_{11}{}^i} + \dfrac{D_{21}{}^e r_0}{3} \right\} \dfrac{1}{\Delta_e} + \left\{ C_2{}^0 - \dfrac{D_{21}{}^i q_1}{D_{11}{}^i k_2} \right\} r_0}{\sinh \alpha r_0 + \left\{ \alpha r_0 \cosh \alpha r_0 - \sinh \alpha r_0 \right\} \dfrac{D_{11}{}^i D_{11}{}^e}{\Delta \Delta_e}}, \tag{56}$$

where $\Delta_e = |D_{kj}{}^e|$. The constant B_2 in $C_2{}^e$ is determined from

$$B_2 = A_2 \sinh \alpha r_0 + \left\{ \frac{D_{21}{}^i q_1}{D_{11}{}^i k_2} - C_2{}^0 \right\} r_0. \tag{57}$$

If substance 2 is consumed, sinh and cosh are replaced by sin and cos. If $q_1 < 0$, then $A_2 > 0$ and it increases linearly with $|q_1|$; A_2 also increases with $D_{21}{}^i$ but the dependence is not simple since $D_{21}{}^i$ appears in α and Δ.

Thus the rate of consumption, per unit volume, of substance 2 is influenced by the presence and the rate of consumption of substance 1 due to a) the influence of the additive term, b) the dependence of A_2 on q_1 and $D_{21}{}^i$ and c) the dependence of β upon $D_{21}{}^i$.

When $q_1 < 0$ there are restrictions on $C_2{}^0$ such that $C_2{}^i > 0$ for $0 \leq r \leq r_0$; these limit the permissible dependence of A_2 upon D_{12} and D_{21}.

In an entirely similar manner it can be shown that if substance 1 is consumed at a rate proportional to its concentration and substance 2 is produced at a rate proportional to $C_1{}^i$, the rate of the reaction is determined among other factors by the presence of the product (substance 2) and by the external concentration, $C_2{}^0$ of the product. Thus the concentration of product in the medium influences the rate of a kinetically irreversible reaction: i.e. a reaction infinitely far from equilibrium. Consider the set

$$\left.\begin{aligned} \sum_{j=1}^{2} D_{1j}{}^i \nabla^2 C_j{}^i &= k_1 C_1{}^i, \\ \sum_{j=1}^{2} D_{2j}{}^i \nabla^2 C_j{}^i &= -k_1 C_1{}^i, \end{aligned}\right\} \tag{58}$$

which describes the production of substance 2 from substance 1 by a first order irreversible reaction. The solutions are found, from (17), to be

$$C_1{}^i = A_1 \frac{\sinh \alpha r}{r}, \tag{59}$$

$$C_2{}^i = A_2 - \left(\frac{D_{11}{}^i + D_{21}{}^i}{D_{22}{}^i + D_{12}{}^i} \right) A_1 \frac{\sinh \alpha r}{r}, \tag{60}$$

where $\alpha = \sqrt{k_1 (D_{22}{}^i + D_{12}{}^i)/\Delta}$. From the boundary conditions

$$\left.\begin{aligned} C_2{}^i &= C_2{}^e \quad \text{at} \quad r = r_0, \\ -k_1 \int_V C_1{}^i \, dV &= \vec{n} \cdot \vec{J}_1{}^e, \\ \vec{n} \cdot \vec{J}_2{}^i &= \vec{n} \cdot \vec{J}_2{}^e, \end{aligned}\right\} \tag{61}$$

the quantity A_1 is determined as

$$A_1 = \frac{r_0 C_1^0}{\sinh \alpha r_0 + \frac{\Delta}{\Delta_e} \frac{D_{22}^e + D_{12}^e}{D_{22}^i + D_{12}^i} \left(\alpha r_0 \cosh \alpha r_0 - \sinh \alpha r_0 \right)}; \quad (62)$$

the quantity B_1 from

$$A_1 \sinh \alpha r_0 - C_1^0 r_0 = B_1 . \quad (63)$$

As the coefficients D_{12}^i, D_{12}^e increase, A_1 decreases (largely due to the increase in α) and the greater the "drag" of the product upon the reactant, the slower the rate of reaction: If $D_{12}^i = D_{21}^i = D_{12}^e = D_{21}^e = 0$, no constants referable to substance 2 appear in A_1.

In summary then, an inert solute, or simultaneous but independent chemical reactions may influence the rate of a given reaction and the diffusion properties of the *product* modify the rate of an *irreversible* reaction.

Distribution of a catalyst.

Granting that a *given* solute is distributed in the cell according to the flows and productions of all other solutes, one may ask in particular for the distribution of catalytic particles. Such particles are conserved in the cellular reactions, and under steady state conditions their rate of production is zero (provided no *synthesis* of new particles is occurring when no steady state is possible). Their distribution is determined by the currents, $\vec{J}_k^i$, of all other solutes; these currents are in turn conditioned by the metabolic rates which in turn are determined by the concentration of catalyst. With simplifying assumptions this problem fails in biological importance for the intuitive supposition is verified that if the "drag of outflowing solutes" predominates, the catalyst is concentrated at the periphery of the cell and conversely.

Consider for example the set

$$\left.\begin{aligned} \sum_{j=1}^{2} D_{1j}^i \nabla^2 C_j^i &= 0, \\ \sum_{j=1}^{2} D_{2j}^i \nabla^2 C_j^i &= -k_2 C_1^i, \end{aligned}\right\} \quad (64)$$

which describes a substance being produced at a rate *proportional to the concentration of catalyst* (substance 1). From (17), $\nabla^2 C_1^i$ is integrable giving

$$C_1^i = A_1 \cdot \begin{cases} \dfrac{\sinh \alpha r}{r} \\ \dfrac{\sin \alpha r}{r} \end{cases}, \qquad (65)$$

where $\alpha = \sqrt{D_{12}^i |k_2| / \Delta}$ and the sinh form holds for $k_2 > 0$. Substitution of C_1^i from (65) into $\nabla^2 C_2^i$ from (17) gives

$$C_2^i = A_2 - A_1 \frac{D_{11}^i}{D_{12}^i} \cdot \begin{cases} \dfrac{\sinh \alpha r}{r} \\ \dfrac{\sin \alpha r}{r} \end{cases}. \qquad (66)$$

The distribution $C_1^i(r)$ of the catalyst simulates that of a substance which obeys the *simple* Fick's Law, is produced at a rate $k_2 C_1^i$ and exhibits a diffusion coefficient Δ / D_{12}^i. Either of the forms (65) is also observed if several substances are involved. For example if $q_1 = 0$, $q_2 = -k_2 C_1^i$, $q_3 = k_2 C_1^i$, $k_2 > 0$, i.e. substance 2 is converted to substance 3 at a rate proportional to the concentration of catalyst, then

$$\nabla^2 C_1^i = C_1^i k_2 [R_{12} - R_{13}], \qquad (67)$$

and $r C_1^i$ is of the form sin αr or sinh αr depending upon the signs and magnitudes of the reduced cofactors R_{12}, R_{13}. The catalyst is not necessarily concentrated toward the periphery or center when there is a net outflow or inflow of material

$$\left(\sum_k \int_V q_k \, dV \gtrless 0 \right)$$

respectively: The distribution is determined by the relative values of the D_{kj}^i of the outflowing and inflowing solutes. In the case described by (67) there is clearly no net outflow of material for

$$\sum_k \int_V q_k \, dV = 0.$$

It is not difficult to show that for s solutes with $q_k = 0$, $k = 1, 2, \cdots s/3$ for every catalyst and $q_k = -q_{k+1} = k_k C_1^i$, $k > s/3$, for every product-precursor pair, the conclusion from (67) is general. It will be obvious that whatever the spatial distribution of the catalyst, the *total* rate of the catalyzed reaction is the same. It is in fact kn where n is the total number of moles of catalyst, $\int_V C_1^i \, dV = n$.

The A_1 of (65) or the constant of integration in the solution of (67) is determined by this condition of conservation of catalyst. This conclusion regarding the equality of total rate for any catalyst distribution and conclusions from (64) and (67) [that $C_1{}^i(r) = (\sinh \alpha r)/r$ or $(\sin \alpha r)/r$] are not true if the rates are *not* proportional to the catalyst concentration, e.g. if $q = k(C_1{}^i)^2$, $q_j = k\, C_1{}^i\, C_j{}^i$, etc. A *physically* simple example is

$$\left.\begin{aligned} \sum_{j=1}^{2} D_{1j}{}^i \nabla^2 C_j{}^i &= 0, \\ \sum_{j=1}^{2} D_{2j}{}^i \nabla^2 C_j{}^i &= -k_2\, C_1{}^i\, C_2{}^i. \end{aligned}\right\} \tag{68}$$

The first of these equations requires that

$$D_{11}{}^i\, C_1{}^i + D_{12}{}^i\, C_2{}^i = A = \text{const.} \tag{69}$$

and using (69) and (17) gives,

$$\nabla^2 C_1{}^i = K_1\, C_1{}^i - K_2\, C_1{}^i\, C_1{}^i, \tag{70}$$

where $K_1 = k_2\, A/\Delta$, $K_2 = k_2\, D_{11}{}^i/\Delta$. If n is small then $C_1{}^i$ obeys approximately

$$\frac{d^2(r\, C_1{}^i)}{d\, r^2} = K_1\, r\, C_1{}^i - \frac{K_3}{r}\, \phi^2(r), \tag{71}$$

where $\phi(r) = \sinh \alpha r$ or $\sin \alpha r$ if $k_2 > 0$ or $k_2 < 0$, $\alpha = \sqrt{|K_1|}$ and K_3 is K_2 times an arbitrary constant. The solution of (71) cannot be obtained in closed form. An approximate solution is, for $k_2 > 0$,

$$\left.\begin{aligned} r\, C_1{}^i &= A_1 \sinh \alpha r - \frac{K_3}{4}\left\{ f(r) + \sum_{n=1}^{\infty} \frac{1}{(-\alpha)^n} \frac{\partial^n f(r)}{\partial\, r^n} \right\}; \\ f(r) &= \sum_{j=1}^{\infty} a_j\, r^j, \quad a_j = \frac{1}{\alpha} \frac{\alpha^j + (3\alpha)^j - 2(-\alpha)^j}{j \cdot j!}; \end{aligned}\right\} \tag{72}$$

while the difficulties of the diffusion equation forbid a concise assessment it is clear that in physically realistic cases a catalyst may exhibit a distribution different from $A(\sinh \alpha r)/r$ or $A(\sin \alpha r)/r$ and that the total rate, $\int_V q\, dV$, of the catalyzed reaction will depend upon the spatial distribution of the catalyst. The importance of coupling by diffusion is *greatly enhanced* by the possibility of distributing catalysts in the resultant diffusion field of reactants, products and catalysts.

Non-Isothermal Systems.

The equations of transport for non-isothermal systems are available (Eckart, 1940; Leaf, 1946). A few remarks relevant to metabolizing systems will be made. It is probable that the gradients in temperature due to gradients in composition (inverse Soret effect) are small and that the effects of thermal diffusion are likewise negligible under these conditions. However a system in which chemical reactions are occurring must be treated as having continuously distributed sources and sinks of heat. The temperature gradients due to this effect are probably important. This effect may be included in the problem as follows: In equations (10), (15) and (16) let the summations run from $j = 0$ to $j = s$ and let $\vec{J}_0$ be the vector of heat flow. Then D_{k0} will be the coefficients of thermal diffusion, D_{00} the coefficient of thermal conductivity and D_{0k} the "inverse Soret coefficients." For q_0, the production per unit volume of heat, we have

$$q_0 = \sum_{k=1}^{s} \tilde{H}_k \, q_k ,$$

where $\tilde{H}_j$ is the partial molal enthalpy of the jth solute. By expressing the q_j from the usual kinetic expressions q_0 may be written (Hearon, 1950a, b) as

$$q_0 = \sum_{j=1}^{n} \Delta H_j \, v_j ,$$

where ΔH_j is the heat of reaction and v_j the velocity for the jth chemical reaction. Similarly, in equations (30), h_{k0} and h_{0k} are the coefficients of thermal diffusion and the inverse Soret coefficients in the membrane and h_{00} the heat conductivity of the membrane. Strictly speaking the q_j and v_j are, through the temperature, functions of the space coordinates and similarly for the ΔH_j which are temperature dependent. This complicates matters considerably but some of the problems involved in simple cases have been solved by W. S. Horton (1948). It might be predicted that if $q_0 > 0$, including heat flow in the problem will have about the same effect as an additional solute produced at the rate q_0 and exhibiting cross coefficients D_{0k}, D_{k0}, $k = 1, 2, \cdots s$. There would be superimposed upon the effect of coupling by diffusion the effect of "coupling by thermal diffusion." It may then be possible to attribute special roles, of maintenance of non-equilibrium distributions and of coupling, to reactions with conspicuously large ΔH's. A further implication is that the temperature dependence of reaction rates in the intact cell would be

a composite affair including the effects of coupling by diffusion and thermal diffusion as well as the innate temperature dependence of rate processes. Also to the extent that such effects are measurably important the frequently determined increase in heat production above the "resting level" or "non-nutrient level" will be a complex quantity.

Discussion.

It may be briefly pointed out that *few* cases can be solved when the q_k are functions of several $C_j{}^i$. When the q_k are *linear* combinations, $\sum_j k_{kj} C_j{}^i$, many such problems may be solved. Such a linear combination suffices, for example, to describe a series of first order consecutive reactions and it is easily shown that the determinantal equation to be solved is *always* reducible to degree 2 $(s-1)$.

The expressions used for the q_k in this paper for discussing the distribution of a catalyst are most inadequate and the situations discussed highly oversimplified. In general the rate of a catalyzed reaction is proportional neither to the concentration of catalyst nor to the product of the concentrations of catalyst and reactant (Hearon, 1949). In *simple* cases the above are limiting cases for very high or very low concentration of reactant: In general this is only approximately true (Hearon, 1949).

An important consequence of Onsager's Generalization is that *inert* solutes may have non-zero gradients and different cellular and environmental concentrations. Thus inert solutes *can* contribute to osmotic forces and to diffusion drag forces [if the magnitude of these forces be taken as proportional to the gradient (Rashevsky, 1948; Landahl, 1942)]. Quite different expressions for the force components in "Betti's Theorem" treatment of cell elongation (Young, 1939; Rashevsky, 1948) result from these considerations.

It has been found possible for metabolized solutes to flow against their own gradients and for *inert* solutes to flow into a region of higher concentration from one of lower concentration (cf. discussion Hearon, 1950b). We wish to point out here the similarity between these situations, direct consequences of equation (10), and those cases treated by J. Frank and J. Mayer (1947, especially their discussion pp. 301–302) and the "diffusion retrograde" discussed by T. Rosenberg (1948).

Finally, in addition to the implications already mentioned which equation (10) has for the permeability concept, it would seem that attempts to compute absolute permeabilities (Bloch, 1944) must pro-

ceed along fairly different lines to the extent that the cross coefficients are important.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 12, 1950

ON THE REMOVAL OF AIR-BORNE DROPLETS BY THE HUMAN RESPIRATORY TRACT: II. THE NASAL PASSAGES*

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Theoretical considerations lead to the calculation of the amounts of air-borne materials removed by the various regions of the human nasal passages. These calculations are presented and discussed in the light of available data and lead to the conclusion that impaction due to inertia is the principle factor in the removal of the air-borne particles of diameters greater than one micron.

In considering the mechanisms by which particles may be removed from the air stream as they pass through the nasal passages (cf. Proetz, 1941; Davies, 1946), one is led to the evaluation of the following: impaction on the inner walls, impaction on the nasal hairs, settling and diffusion. For all flow rates, and for particles greater than one-tenth of a micron, calculations show that the effect of diffusion is negligible compared with the effect of settling.

Schematic Representation of the Nasal Passages. In order to make the calculations we adopt the following schematic description for the nasal passages. Each of the external nares (A) is taken to have a cross-sectional area of 0.75 cm.^{2}, with hairs of about 100 micron diameter occupying one-half of the projected area. The projected area of an object is the area of its projection on a plane perpendicular to the direction of air flow. The projected area of the hairs was estimated in one subject by comparing the blackness of discs of photographic paper placed behind the hairs. Another estimate was made by removing all the nasal hairs possible and measuring the lengths (total length ca. 50 cm.) and diameters. The hairs taper and vary greatly in diameter. The variability can be taken into account to a first approximation by considering the hairs to be of two sizes, one of 70 and one of 130 microns in diameter, each group occupying one-fourth of the projected area.

*The work described in this paper was done in part under contract between the Medical Division, Chemical Corps, U. S. Army, and The University of Chicago Toxicity Laboratory. Under terms of the contract the Chemical Corps neither restricts nor is responsible for the opinions or conclusions of the author.

The second region (B) is the constriction about 2 cm. behind the opening of the external nares at the end of the nasal bones. This we take to be a rectangular tube 1.2 cm. high and .25 cm. wide which bends at an angle (θ_B) of 30°. The length of the region is about 1 cm.

The third region (C) is taken to be equivalent to a rectangular tube 2mm. wide, 3 cm. high and about 1 cm. long, in which there is a bend of about 20° (θ_C).

The fourth region (D) will be sub-divided into two regions which are connected in parallel, one representing the somewhat narrower (1 mm.) and more tortuous upper passages, the other the wider (2 mm.) and more direct lower passages. Thus region D is represented by a rectangular tube whose width is from 1 to 2 mm., height about 4 cm., and length about 5 cm., so that the total effective wall area for both nasal passages is about 80 cm.^{2} Thus we assume, on the average, nearly two-thirds of the total area (Hellmann, 1927) is functional at any particular time. In the upper region some parts of the air stream may make several fairly sharp bends. In the lower region some parts of the air stream make only a slight bend. We shall consider the upper air stream to make the equivalent of one change in direction, the angle being about 45°, while the lower part makes an average turn of about 20°. Furthermore, we shall consider our schematized region D to be orientated at an angle of about 45° from the vertical ($\psi = 45°$). We shall make the calculations for the case in which half of the flow is through passages 1 mm. and half through passages of 2 mm., the proportions of the height pertaining to each being in the ratio 3 to 1. The results are rather insensitive to the value of this ratio.

The order of magnitude of the pressure drop for the model is the same as that observed in the subjects used in the experiments to be discussed.

Removal by Impaction on Nasal Hairs. The fraction of particles moving toward a cylindrical object which is removed by impingement depends upon the inertia and sizes of the particles and the size of the object. We introduce the following notations: The quantities f' and f'' are the fractions of the projected area covered by the two groups of nasal hairs (one-fourth for each group), ρ and d are the particle density and diameter (cm.), V is the average velocity of the air stream (cm./sec.) and D' and D'' are the diameters (cm.) of the two groups of hairs. Then the fraction of particles entering the nose which impacts against the nasal hairs can be written as the

sum of two similar terms P_h' and P_h'', one for each group of hairs. Thus we write the equation (Landahl and Herrmann, 1940)

$$P_h' = f' \left[\frac{150\ (\rho\, d^2 V/D')^3}{3 \times 10^{-6} + (\rho\, d^2 V/D')^2 + 150\ (\rho\, d^2 V/D')^3} + \frac{d}{D'} \right]. \qquad (1)$$

The expression for P_h'' is obtained from expression (1) by replacing f' and D' by f'' and D''. To obtain V, the flow rate F (cc./sec.) through both nostrils is divided by twice the area of each nostril. Since the velocity distribution is actually not constant, we shall take this into account, to some extent, by increasing the variability in hair diameter. Thus in the calculations the D's are taken to be 50 and 150 microns respectively. The total probabilty, P_h, if the hairs were regularly spaced, would be the sum of P_h' and P_h'' for the two groups, since these processes are mutually exclusive. To take into account the irregular spatial distribution of the nasal hairs, we shall introduce $P_A = 1 - e^{-P_h}$ as the net probability of removal in region A.

Removal by Impaction Within the Passages. For the probability of impaction in bent tubes with parallel walls, and in the absence of turbulence, we may derive an expression in the following way. Let θ be the angle of the bend. Consider a particle at a distance y from the center of the stream approaching the bend. In order to reach the outer wall, the particle must slip a distance $(W/2 - y)$ cosec θ perpendicular to the direction of the air stream. A more detailed calculation for $\theta = \pi/2$ shows that the slip is only slightly greater than that which would occur if the particle was shot with the same velocity into quiet air (cf. Landahl and Herrmann, 1950, Appendix). We shall ignore this discrepancy. By Stoke's Law, the distance that a particle travels through quiet air is $\rho\, d^2\, Vy/18\, \eta$ ($\eta = 1.8 \times 10^{-4}$ poise) when its initial velocity is V_y. Since the velocity distribution is parabolic and the velocity is zero at the walls, $V_y = 1.5V\ (1 - 4y^2/W^2)$. If this distance of slip perpendicular to the air stream for a particular position $y = y^*$ is set equal to $(W/2 - y^*)$ cosec θ, then the resulting equation determines this particular y value so that no particle which has a position $y < y^*$ before reaching the bend can reach the outer surface. If we solve for y^* we obtain

$$y^* = \frac{1}{3} \frac{18\, \eta\, W}{\rho\, d^2\, V \sin \theta} - 1. \qquad (2)$$

The fraction I' of particles removed is then obtained by integrating $V_y\, dy$ from y^* to $W/2$ and dividing by the same integral but with the

limits $-W/2$ and $W/2$. If $\rho\, d^2\, V \sin\theta \geqslant 3\,\eta\, W$, we find the following expression for the fraction of the air-borne particles removed at a bend when the flow is smooth:

$$I' = 1 - \frac{1}{12}\left(\frac{18\,\eta\, W}{\rho\, d^2\, V \sin\theta}\right)^2 + \frac{1}{108}\left(\frac{18\,\eta\, W}{\rho\, d^2\, V \sin\theta}\right)^3 . \qquad (3)$$

If $\rho\, d^2\, V \sin\theta \leq 3\,\eta\, W$, then $I' = 0$.

On the other hand, if all the particles moved with uniform velocity, they would be displaced uniformly perpendicular to the air stream as they passed the bend, and the per cent arriving at the outer surface would be proportional to $\rho\, d^2\, V \sin\theta/W$. When $\rho\, d^2\, V \sin\theta/18\eta = W$, the innermost particles would have just reached the outer wall. Hence the fraction I'' removed under these conditions is given by

$$I'' = \frac{\rho\, d^2\, V \sin\theta}{18\,\eta\, W} = 300\,\frac{\rho\, d^2\, V \sin\theta}{W} \qquad (4)$$

unless the quantity on the right is greater than unity, in which case I'' is equal to unity. In regions B, C and D the Reynold's numbers are about 10^3 to 10^2 for flow rates under consideration. Since the lengths are relatively short and the passage walls are uneven, the flow cannot be expected to be smooth. We shall, therefore, use the average of the values obtained from equations (3) and (4).

Removal by Sedimentation. This effect will be considered only for the region D. It is appreciable only at small flow rates. For the calculations we shall use equation (4) of a previous paper (Landahl, 1950), with the following change. If every air-borne particle in a horizontal cylinder fell vertically a distance equal to the cylinder radius, 61% of the particles would reach the bottom surface; in a slot the corresponding percentage would be 50. Thus instead of 2.3 $\cos\psi$ we shall use $2.3 \times (0.50/061)\cos\psi = 1.9\cos\psi$. Let τ be the mean time for the air to pass through region D. Then, except for particles of diameter considerably less than 1 micron, we may write as follows for the fraction settling in region D,

$$S = 1 - e^{-3.8\times10^5\rho d^2\tau\cos\psi/W}. \qquad (5)$$

Let A_t be the surface area of region D. The quantity F is the flow through both sides of the turbinates, W is an average width of this region. Since $F = 2H\ W\ V$, $\tau = L/V$ and $A_t = 4HL$, where H and L are the height and length of the region, the time of passage can be written as

$$\tau = A_t W/2F. \tag{6}$$

Introducing this value for τ in equation (5), we find, since angle $\psi = 45°$,

$$S_d = 1 - e^{-7.6\times10^6 A_t \rho d^2/F}. \tag{7}$$

Calculation of Total Removal. For region A the net probability of an air-borne particle being removed is $P_A = 1 - e^{-P_h}$, where $P_h = P_h' + P_h$, the sum of the probabilities for the two groups of nasal hairs, if we neglect impaction in this region. For regions B and C, $P_B = I_B$ and $P_C = I_C$, since only impaction is considered in these regions. For region D we have $P_D = I_D + S_D - I_D S_D$. Thus the total probability of removal can be written:

$$P_T = 1 - (1 - P_A)(1 - P_B)(1 - P_C)(1 - P_D). \tag{8}$$

The amounts removed in the various regions may also be obtained.

TABLE I

CALCULATED PERCENTAGES OF MATERIAL REMOVED IN VARIOUS PARTS OF THE NASAL PASSAGES FOR DIFFERENT PARTICLE SIZES

Diameter microns (Imp. Eq.)	Region A (Nasal Hairs)	Region B	Region C	Region D	Total (ρ=1)	Total (ρ=1/9)
			(4.5 l/min.)			
2	2	0	0	1	3	6
5	9	1	1/2	3	14	20
10	25	3	1	10	39	46
20	40	22	2	21	86	89
30	47	40	4	8	99	99
40	52	47	1	1/2	100	100
			(18 l/min.)			
1	1	0	0	0	1	2
2	4	1	0	1	6	8
3	11	1	1	2	14	17
5	23	3	1	3	30	34
7	31	5	2	10	48	53
10	36	23	3	16	78	81
15	42	44	5	7	98	99
20	45	53	1	0	99.9	99.9
25	48	52	0	0	100	100
			(72 l/min.)			
1	3	1	0	1	5	6
2	17	2	1	2	22	23
5	39	21	2	14	77	78
10	41	57	1	1	99.9	99.9

In region A the proportion is just P_A. In B it is $(1 - P_A)P_B$; in C it is $(1 - P_A)(1 - P_B)P_C$; and in D it is $(1 - P_A)(1 - P_B)(1 - P_C)P_D$. The sum of these can be checked by equation (8).

Since the density and particle diameter occur in the combination ρd^2 with but one exception, one would expect it to be convenient to introduce the quantity $d' = \sqrt{\rho d^2}$ in both the calculations and the handling of data. This quantity has been referred to as an equivalent impaction diameter (Landahl and Tracewell, 1949). This quantity will be used throughout.

Table I gives calculated values for the amounts of various sized particles removed in various regions at three flow rates. These values give some idea of the shift in locus of deposition which can be expected with change in the flow rate. Also, in the last column are values for particles of density of 1/9; these give some idea of the expected effect of change in density, e.g. light flocculent material.

The results of these calculations may be compared with available data (cf. Landahl and Tracewell, 1949). We consider first the effect of the nasal hairs. The comparison is given in Table II.

TABLE II
REMOVAL OF PARTICLES BY NASAL HAIRS
(Flow Rate—18 l/min.)

Cloud Fraction	Diameter (Imp. Eq.)	Calculated Removal %	Observed Removal %
A	13	43	(73)
B	8.7	39	44
C	3.9	27	24
D	2.0	9	2
Imp.	1.1	1	(8)

The comparison for the total removed at 18 l/min. is shown in Figure 1. It will be noted that the principal deviation is that the calculated values of the per cent penetrating the nose are high for particles of about three microns in diameter. If we go to higher flow rates (cf. Landahl and Black, 1947) for corn oil, we see that the shift to smaller sizes is somewhat higher than expected—about two and one-half instead of almost two. Since for flow rates appreciably greater than 18 l/min. sedimentation is negligible, as is the factor d/D in equation (1), the effect of a change in flow rate by a factor of two should be equivalent to a change by a factor of $\sqrt{2}$ in the particle size. It should be pointed out, however, that the reflex changes

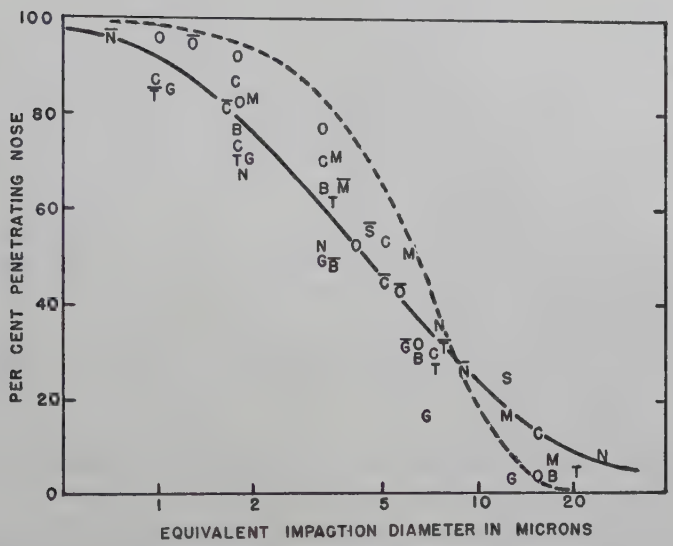

FIGURE 1. Per cent nasal penetration of various air-borne particulates: *O*—corn oil, *N*—$NaHCO_3$, *C*—$Ca_3(PO_4)_2$, *M*—methylene blue, *B*—bismuth subcarbonate, *T*—tyrosine, *S*—Na_2SO_4, *G*—glycerol (Landahl and Tracewell, 1949). Broken line: theoretical curve from calculated values in Table I.

which occur upon marked changes in flow rate, temperature or humidity make it difficult to make accurate comparisons.

The effect of subject variability and variability among subjects would tend to lower the high values and raise the low values where the curvature is great. An estimate of this effect suggests that it is appreciable. Furthermore, the method used (Landahl and Black, 1947) in which cloud fractions are divided, does itself also introduce variability, so that actually for a single subject over a short time, the shape of the curve is more like the shape of the calculated curve. In the case of non-liquid materials, the failure of the particles to adhere perfectly in the sampling instruments adds further variability. Also the failure of some of the particles to adhere to the hairs or the walls of the nasal passages, as well as the possible breaking off of parts of aggregated material, tends to increase the variability. It will be noticed that the corn oil gives the sharpest curve. The points representing glycerol should not be considered. In this case the effect of humidification on such a hygoscopic material cannot be neglected since the particle may increase in size due to absorption of water. Humidification may also play some role in the case of some of the other substances.

We mention, in passing, some factors which have not been considered but which could conceivably influence the percentage removed. If the nasal linings are considered to be sufficiently good conductors, the only way in which the electrical charges on particles could operate to influence removal would be through repulsion between like charges. However, it is likely that, unless a special effort were to be made by the experimenter to reduce the time between formation and sampling of the charged particles, the effect of such repulsion would be spent before the particles reached the nostrils, since the time of passage is a small fraction of a second.

The effect of the temperature gradient in the experiment discussed is probably very small since the actual temperature difference between the incoming and outgoing air was seldom much more than 10°C.

The effect of humidification on the removal of non-hygroscopic particles can be roughly estimated in the following way. For simplicity consider a right angle bend and take a particle at the center of the stream which would, due to impaction, just reach the outer wall. If the humidification were taking place uniformly in region D, then the velocity u of flow perpendicular to the air stream would be $u = q\,F/4H\,L$, q being the fraction of the volume occupied by water vapor. For q we shall take 0.03. Although the actual value is generally somewhat larger, the viscosity of water vapor is smaller than that of air. We shall thus not introduce a change in the viscosity. Instead of a movement by the particle into still air we shall now have a movement into air which is moving in the opposite direction. Thus we have, if the mass of the particle is m,

$$m\ddot{x} = -3\pi\eta d(\dot{x} + u), \tag{9}$$

so that for $x = 0$ and $\dot{x} = 1.5V$ at $t = 0$, we obtain

$$x = -ut + \frac{1.5V + u}{3\pi\eta d} m\left(1 - e^{\frac{-3\pi\eta dt}{m}}\right). \tag{10}$$

If $u = 0$ and $t = \infty$, then $x = x_\infty = \rho(3V/2)d^2/18\eta$, the expression used in obtaining equations (3) and (4).

The maximum distance x_m of slip through the air stream occurs at t^* when the velocity is zero. If the wall is not reached, the particle then begins to turn back because of the velocity u. Setting the velocity equal to zero, solving for t^* and substituting the result into (10) we find the maximum distance of slip to be

$$x_m = x_\infty \left(1 - \frac{2u}{3V} \log \frac{3V}{2u} \right) . \tag{11}$$

Since $F = 2V\ WH$, we find the following expression for the relative error made in neglecting this effect:

$$(x_\infty - x_m)/x_\infty = \frac{qW}{3L} \log \frac{3L}{qW}. \tag{12}$$

If now $q = 0.03$, $L = 5$, $W = 0.15$, then the relative error is 0.002. The relative change in the percentage removal is thus negligible in this case. Where the percentage removal is small, the relative error becomes large, but the net effect is still small.

In the light of the above discussion and in view of the crudeness of the model, the calculated results are fairly satisfactory and are a further demonstration that the principal factor in the removal of air-borne particles by the nasal passages is impaction due to the inertia of the particles.

The author wishes to express his appreciation to Dr. H. B. Perlman, Associate Professor of Otolaryngology, for reading and discussing the manuscript.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 12, 1950

A NOTE ON A THEORETICAL MECHANISM TO REPRESENT THE KINETICS OF SOME ALKALINE PHOSPHATASES

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If an enzyme acts in a manner somewhat different from that generally considered, it may appear to act as a pair of enzymes. This similarity may remain after various changes in the solution such as activation by magnesium ions. Conditions are given under which this type of activity may be differentiated from that of an enzyme pair. Some alkaline phosphatases exhibit the type of time course of hydrolysis under consideration. Available data do not eliminate the possibility that some alkaline phosphatases act in the manner here suggested.

The study of some alkaline phosphatases suggests that two closely associated, inseparable, enzymes are present in these cases (Householder and Gomori, 1943). The purpose of this note is to consider some conditions under which a single enzyme may give results similar to those obtained from such an enzyme pair. We thus consider the following scheme (E = enzyme, OP = organic phosphate; cf. Schwab, 1937, p. 337)

$$E + OP \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} OPE \overset{k_2}{\rightarrow} OE + P;$$

$$OE \overset{k_3}{\rightarrow} O + E\,.$$

We shall consider the last two steps to be irreversible since in this system the addition of products does not have an appreciable effect up to one hundred times the concentrations normally used. Furthermore the concentration of OP is assumed to be constant because only very little material is broken down.

From the above scheme we may write, if $S = [OP]$, $x = [OPE]$, $y = [OE]$ are the corresponding concentrations,

$$\frac{dx}{dt} = k_1 ES - k_{-1}x - k_2 x; \tag{1}$$

$$\frac{dy}{dt} = k_2 x - k_3 y; \tag{2}$$

and the total enzyme concentration is

$$E_0 = x + y + [E]. \tag{3}$$

If we denote by ξ and η the deviations of x and y from their steady state values, we have

$$\xi = x - k_1k_3E_0S/[k_1k_2S + k_1k_3S + k_{-1}k_3 + k_2k_3] \tag{4}$$

and

$$\eta = y - k_1k_2E_0S/[k_1k_2S + k_1k_3S + k_{-1}k_3 + k_2k_3]; \tag{5}$$

then

$$\frac{d\xi}{dt} = -(k_1S + k_{-1} + k_2)\xi - k_1S\eta; \tag{6}$$

$$\frac{d\eta}{dt} = k_2\xi - k_3\eta. \tag{7}$$

Thus the solutions for ξ and η are of the form

$$\xi = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}; \tag{8}$$
$$\eta = Ce^{-\lambda_1 t} + De^{-\lambda_2 t}; \tag{9}$$

where

$$\lambda_{1,2} = \tfrac{1}{2}(k_1S + k_{-1} + k_2 + k_3) \pm \tfrac{1}{2}\sqrt{(k_1S + k_{-1} + k_2 + k_3)^2 + (k_2k_3 + k_1Sk_3 + k_1k_2S + k_{-1}k_2)}. \tag{10}$$

Experiments are generally carried out with rather large amounts of the substrate. Thus if S is very large one of the composite rate constants, λ_1, becomes infinite; the other, λ_2, becomes $k_2 + k_3$. If also, $y = 0$ and $x = E_0$ for $t = 0$, then we find from (3), (4), (6) and (8) that

$$x = \frac{k_3E_0}{k_2 + k_3} + \frac{k_2E_0}{k_2 + k_3}e^{-(k_2+k_3)t}. \tag{11}$$

Since the rate of production of inorganic phosphate is k_2x, we have for the total amount of inorganic phosphate $[P]$ at the time t, if $\alpha = k_2 + k_3$ and if $[P] = 0$ for $t = 0$,

$$[P] = \frac{k_2k_3E_0t}{\alpha} + \frac{k_2^2E_0}{\alpha^2}(1 - e^{-\alpha t}). \tag{12}$$

If we set

$$x_\tau = k_2 \frac{k_2 E_0}{k_2 + k_3}, \tag{13}$$

$$y_\tau = k_3 \frac{k_2 E_0}{k_2 + k_3}, \tag{14}$$

then equation (12) becomes identical with equation (6) of A. S. Householder and G. Gomori. Since generally it was found that $x_\tau >> y_\tau$, this would mean that $k_2 >> k_3$. Thus $\alpha \approx k_2$.

Where the effect of storage (Householder and Gomori, 1943) is such as to affect both components in about the same manner, the interpretation in terms of the present scheme is evident. In cases in which this is not so, it is necessary to suppose that incubation has caused a differential change in the reaction rates.

The effect of magnesium ions on the activity of certain enzyme preparations at low values of the *pH* (ca. 8) can be accounted for by considering that addition of the ions greatly increases the rate constant k_3 but only slightly increases k_2: thus the *"x"* component is apparently inactivated while the *"y"* component appears to be activated. At higher values of the *pH* (ca. 10), both rate constants are slightly increased by magnesium ions.

When the enzyme preparation is incubated for several days with the substrate containing magnesium ions, the activity generally appears to fall off slowly instead of maintaining a constant activity. In terms of the two-enzyme hypothesis, this would be interpreted as meaning that the *"y"* component is very slowly inactivated. In the present scheme it would mean that either of the enzyme complexes containing (or in the presence of) magnesium is inactivated very slowly. Let the inactivation rate constant for the (*OPE*) complex be m^* and let the rate constants in the presence of magnesium ions be denoted by asterisks. In this case we find an expression for the amount (P^*) of inorganic phosphate formed in the presence of magnesium ions in a manner similar to that used to obtain equation (12). Since m^* is very small, we may simplify the expression, in which case we have:

$$[P^*] = \frac{k_2^*}{m^*}\left(1 + \frac{2m^*k^*_3}{\alpha^*}\right)\left(1 - e^{-m^*k^*_3 t/\alpha}\right) + \frac{k^{*2}_2}{\alpha^{*2}}\left(1 - \frac{2m^*k^*_3 + m^*k^*_2}{\alpha^{*2}}\right) \times \left(1 - e^{-(\alpha^* + m^*k^*_2/\alpha^*)t}\right). \tag{15}$$

This expression is entirely similar to that which is obtained when

the "y" component is taken to be inactivated [Householder & Gomori, 1943, equation (5)]. However, the interpretation of the data may be simpler in terms of one of the hypotheses.

We next consider the possibility of differentiating between the two hypotheses by experiments involving addition of a tagged substrate at various times τ' with subsequent determination of the rate of hydrolysis of this substrate at the time of its addition. Suppose that k_1 and k_{-1} are much greater than any other rate constant. Then if the new substrate S' is added in such an amount that after addition the concentrations of S' and S are in the proportion $S' = RS$, then we will have $x' = Rx$, the primes denoting the tagged molecules. Since $\{d[P']/dt\}_{\tau'} = k_2 x'$, the rate is also equal to $k_2 Rx_{\tau'}$ and thus $\{d[P']/dt\}_{\tau'} = R\{d[P]/dt\}_{\tau'}$.

Experiments show that phenylphosphate and β-glycerophosphate appear to be almost interchangeable for one enzyme preparation. Thus suppose that the enzyme preparation has been incubated, with and without magnesium ions, for a time τ' with β-glycerophosphate as substrate. Then the addition of phenylphosphate at time τ' allows one to determine the amount of phenol produced within a short time after τ' and thus $\{d[P']/dt\}_{\tau'}$ is calculated. But since this is equal to $R\{d[P]/dt\}_{\tau'}$, this measured rate is just a measure of the slope of the original curve at time τ'. If k_1 and k_{-1} are not sufficiently rapid this interpretation cannot be used. The ratios of the rates obtained with and without magnesium are the magnesium activation ratios for the corresponding times τ'. Experiments of this kind (Gomori, personal communication) show that the rate $\{d[P']/dt\}_{\tau'}$ is large for small τ' and it decreases to a small constant value in about the expected manner. In the presence of magnesium ions the rate is about fifty per cent larger initially and decreases thirty per cent in twenty-four hours. The magnesium activation was about forty-four per cent for the first hour and slightly over seven fold at twenty-four hours. This can be accounted for in the present hypothesis by setting $k^*_2/k_2 = 1.1$ and $k^*_3/k_3 = 10$, since $\alpha \approx 0.9$ hr^{-1} and $k_2/k_3 \approx 20$.

It can be seen from the reaction scheme that, if the substrate is removed, "x" and "y" are eventually converted back to E. To insure that this will take place, the solution of enzyme and substrate should be dialyzed, for a time much greater than $1/k_3$, against the same buffer used for the hydrolysis and without change in temperature. This time, $1/k_3$, is roughly equal to $(x_\tau/y_\tau)\ (1/\alpha)$. If the time of dialysis is τ'', then upon the addition of substrate equation (12) again holds, but with x_τ replaced by $x_\tau(1 - e^{-k_3\tau''})$. Since $1/\alpha$ is not

more than a few hours while x_τ/y_τ is not likely to be much more than one hundred, the original situation should be restored after a few weeks.

In a preliminary experiment, which was part of a program to test the hypothesis presented here (Gomori, personal communication), enzyme preparations were allowed to act upon the substrate for a time much greater than at after which they were dialyzed up to four weeks against distilled water. The addition of buffer and substrate resulted in a curve for the hydrolysis which, after a twenty minute delay, showed a slight inflection and then continued to rise at a constant rate typical of the "y" component. However until the results of experiments are available, in which the dialysis is against the buffer, it is not possible to exclude the possibility that, in the case of this type of alkaline phosphatase, a single enzyme is acting in a manner, as here suggested, so as to appear to be two components.

The author wishes to express his appreciation to Drs. G. Gomori and J. Z. Hearon for reading and discussing this paper.

This work was aided by a grant from the New Land Foundation to the University of Chicago.

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